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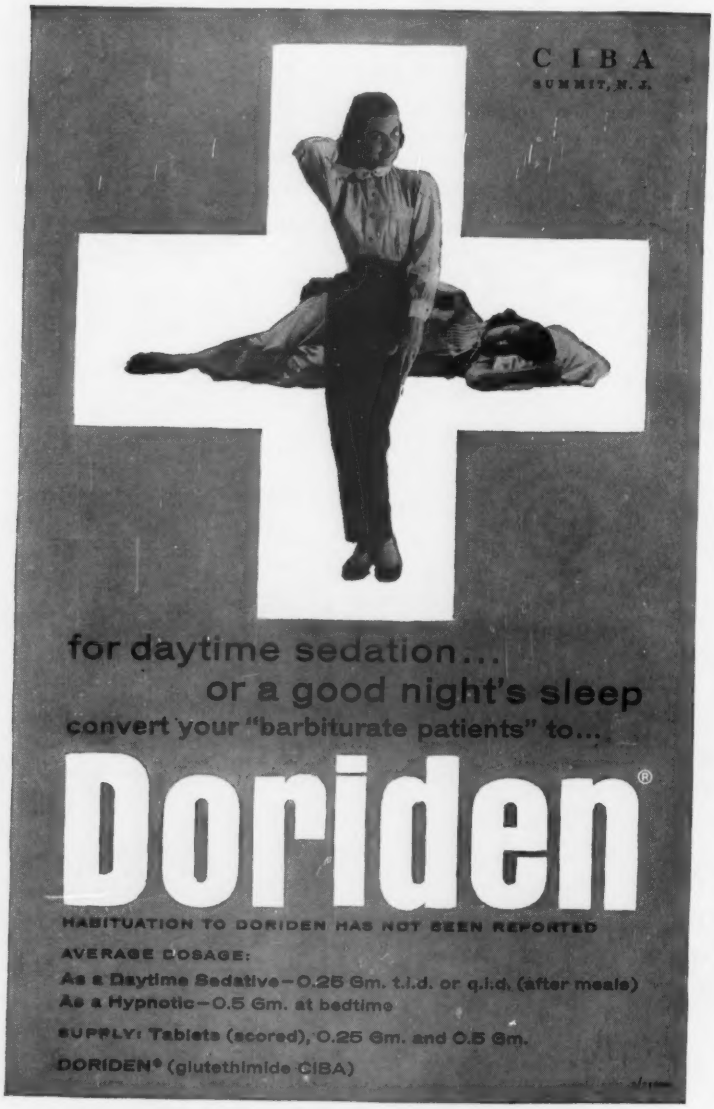
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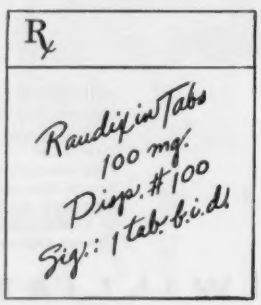

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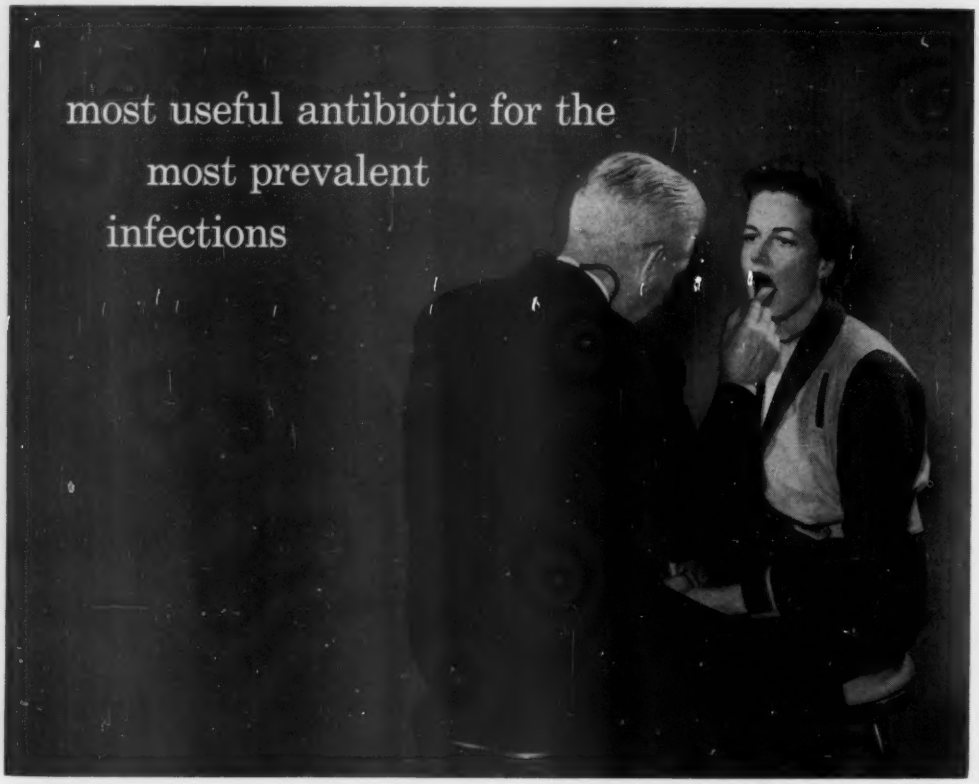

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Volume 253 DECEMBER 22, 1955 Number 25

TREATMENT OF "HEPATIC COMA" WITH L-GLUTAMIC ACID*

WILLIAM V. MCDERMOTT, JR., M.D.,† JOAN WAREHAM, B.A.,‡ AND ATHOL G. RIDDELL, M.B., F.R.C.S.§

BOSTON

THE term "hepatic coma" is used in this report to refer to patients with diseases of the liver or portal circulation who manifest varying degrees of encephalopathy. The term itself is confusing because by no means all the patients who have diseases of the liver and portal circulation and who also evidence varying degrees of central-nervous-system disturbance will actually progress to a comatose state. Nevertheless, the term "hepatic coma" has been in such general use for so long that it is justifiable to continue this custom.

From the point of view of the etiologic factors involved "hepatic coma" has long been a confused and confusing clinical syndrome. A possible relation between hepatic encephalopathies and nitrogenous intake was indicated when Pavlov and his associates[1] described the occurrence of "meat intoxication" in the Eck-fistula dog. Monguió and Krause[2] described elevated levels of blood ammonia in association with "meat intoxication," and studies from this laboratory have shown that ammonia intoxication is in fact the cause of this encephalopathy.[3]

The role of disordered ammonia metabolism in relation to similar encephalopathies in man has been of increasing interest. As long ago as 1927 Burchi[4] suspected that ammonia intoxication might be the cause of neurologic symptoms in a patient with cirrhosis of the liver. In 1932 Van Caulaert and his co-workers[5-8] presented a series of reports in which they were able to induce central-nervous-system symptoms in patients with cirrhosis by the administration of ammonium chloride. A few years later Kirk[9] investigated this problem from a different standpoint and demonstrated that urea synthesis in a great majority of patients with cirrhosis of the liver was entirely normal and that ammonia intoxication, if it occurred, must have been due to the development of a collateral circulation between the portal and systemic systems. For some reason interest in this particular phase of liver disease lagged for over fifteen years. In 1952 Davidson and his colleagues,[10,11] in this country, and Stahl et al.,[12,13] in France, revived the interest in this capacity of nitrogenous substances to induce central-nervous-system symptoms in patients with liver disease. These reports provided the stimulus for studies on a patient in this hospital who was experiencing recurrent episodes of confusion and stupor that followed a portacaval shunt constructed after the portal vein had been resected for cancer of the head of the pancreas.[14] These studies delineated the specific syndrome of ammonia intoxication related to the ingestion of nitrogenous substances, in the presence of a portacaval shunt. Subsequent studies in this laboratory[15-17] have confirmed these observations in a number of other patients with varying types of disorders of the liver or portal circulation, although it is apparent that not all patients with liver disease and concurrent central-nervous-system symptoms will show the same type of disorder in ammonia metabolism.

With renewed interest in this particular phase of liver disease a number of other reports have appeared confirming the observations that encephalopathies of liver disease appear to be associated with disorders in ammonia metabolism.[18-26] In some of these reports it has been apparent that the investigators have been disturbed by the fact that there is not invariably an exact correlation between the actual level of ammonia in the peripheral venous blood and the status of the sensorium in the patient. The question then arises whether or not one can refer to all cases of encephalopathies in liver disease as examples of ammonia intoxication. There is no question that a concept of this sort would be an oversimplification, and in this particular study the clinical material has been divided into various groups on the assumption that all these encephalopathies do not necessarily represent the same basic metabolic disturbance. When a heavy

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nitrogenous load is introduced into the gastrointestinal tract in the presence of a compensated liver, ammonia intoxication may be the sole significant factor. In the cases with progressive, spontaneous decompensation of liver function many factors are involved in producing the attendant clinical syndrome, and disturbances in ammonia metabolism represent only one facet of a complicated metabolic derangement. The working hypothesis of ammonia intoxication, however, provides a rational basis for the treatment of these encephalopathies with L-glutamic acid. This interesting amino acid has long been known to be of specific importance in the metabolism of the central nervous system. In 1935 Krebs[27] found that brain slices were able to synthesize glutamine from glutamic acid and ammonia in the presence of glucose, at a fairly rapid rate. Weil-Malherbe[28] also showed that brain slices could cause added ammonia to disappear in the presence of glucose and that in every case the disappearance of ammonia was roughly accounted for by the synthesis of glutamine. Sapirstein,[29] in 1943, could prevent convulsions induced in rabbits by intravenous ammonium chloride if the rabbits were pretreated with glutamic acid. In 1950 Weil-Malherbe[30] developed the thesis of the ammonia-binding function of glutamic acid in prevention of toxicity with the ammonium ion.

TABLE 1. *Total Experience in the Use of L-Glutamic Acid in the Treatment of "Hepatic Coma."**

TYPE OF ENCEPHALOPATHY	NO. OF PATIENTS TREATED	NO. OF PATIENTS SHOWING IMPROVEMENT	NO. OF IMPROVED PATIENTS RESTORED TO NORMAL NEUROLOGIC STATUS	NO. OF PATIENTS DYING IN HEPATIC COMA	NO. OF PATIENTS DYING OF OTHER CAUSES	NO. OF PATIENTS SURVIVING
Acute spontaneous	6	2	0	6	0	0
Acute exogenous	14	9	5	5	5	4
Chronic	8	7	6	0	2	6

*Neurologic symptoms associated with portacaval shunts or with liver disease.

In 1953 a report by Walshe[31] on the apparent value of glutamic acid treatment in 5 episodes of hepatic coma in 3 patients stimulated increasing clinical use of this amino acid. Since then several publications have appeared on the use of glutamic acid in "hepatic coma" with somewhat conflicting opinions and impressions.[15,16,32-42]

In this study an attempt has been made to evaluate the use of glutamic acid in the treatment of 28 patients with varying degrees of encephalopathy associated with disease of the liver or portal circulation.

CLINICAL MATERIAL

Twenty-eight patients with disease of the liver or portal circulation were treated during episodes of encephalopathy with L-glutamic acid. It has seemed reasonable in evaluating these patients to divide them into three separate groups. One group consists of patients with advanced liver disease who had central-nervous-system signs and symptoms without any precipitating factors such as the ingestion of protein, ammonium chloride or urea diuretics, and without evidence of bleeding into the gastrointestinal tract; this particular group is referred to as suffering from acute spontaneous encephalopathy.

The second group is composed of patients with reasonably well compensated livers who had acute episodes of central-nervous-system signs or symptoms, precipitated by a variety of exogenous factors such as gastrointestinal hemorrhage, oral administration of ammonium chloride or high-protein feedings; the common denominator in this group was the introduction into the gastrointestinal tract of a large amount of nitrogenous substances.

The group classified as suffering from chronic encephalopathy includes patients with disease of the liver or portal circulation who evidenced a chronic confused state without any rapid progression to coma and without any apparent spontaneous remissions or exacerbations.

In this particular report no attempt has been made to analyze these patients according to the extent of portacaval shunts or according to the severity of the derangement in liver function by standard laboratory tests. It was thought that the inclusion of this information would confuse rather than clarify an already lengthy tabulation of clinical material.

TABLE 2. *Relation of Therapy with L-Glutamic Acid to Blood Ammonia Level.*

TYPE OF ENCEPHALOPATHY	NO. OF PATIENTS TREATED	NO. OF PATIENTS WITH FALL IN BLOOD AMMONIA	NO. OF PATIENTS WITH RETURN OF BLOOD AMMONIA TO NORMAL LEVELS*	NO. OF PATIENTS WITH BLOOD AMMONIA REMAINING NORMAL AFTER TREATMENT DISCONTINUED
Acute spontaneous	6	4	0	0
Acute exogenous	14	13	7	7
Chronic	8	7	2	0

*Below 100 gamma per 100 cc.

MATERIALS AND METHODS

L-glutamic acid was used in the treatment of all these patients in varying dosage. Orally, it was given in the form of L-glutamic acid powder in some form of liquid medium. When it was necessary to administer the drug parenterally because of the patient's inability to take oral medication, L-glutamic acid was administered as a sodium salt; standard solutions containing 25 gm. of sodium glutamate in a 100-cc. ampoule were administered by the addition of the ampoule to 1 liter of 5 per cent or 10 per cent dextrose

in water. The total sodium content of 25 gm. of sodium glutamate was 169 milliequiv. Because this large amount of sodium ion is not always well tolerated by patients with cirrhosis and ascites, more recent cases have been treated with a mixture of the sodium and potassium salts, which contains 129 milliequiv. of sodium and 40 milliequiv. of potassium in each 25 gm. of the salt.

The degree of encephalopathy in these patients was clinically evaluated and graded from 1 to 4, a grading of 1 representing mild confusion and 2 and 3 representing more severe degrees of cortical aberration, up to 4, which represents deep coma.

Ammonia determinations on these patients were carried out with the use of a previously reported modification[14] of the microdiffusion technic described by Conway. Normal range of blood ammonia according to this method is 40 to 80 microgm. per 100 cc.

Results

The total experience in the use of L-glutamic acid is summarized from the clinical point of view in Table 1. It is readily apparent that in the group of patients classified under acute spontaneous encephalopathy there was relatively little ultimate value from the treatment although transient improvement was noted in 2 cases. In the acute exogenous and chronic encephalopathies, however, a distinct improvement was noted in the majority of the cases, and over half the patients in these combined groups were restored to a completely normal neurologic status. Table 2 summarizes the effect of treatment with L-glutamic acid on the level of blood ammonia. In all but 4 of the total number of 28 patients there was at least a transient fall in the level of peripheral blood ammonia during and immediately after treatment with glutamic acid. It is apparent from this simplified table, however, that the treatment was much less effective in the patients with so-called acute spontaneous encephalopathy than in the other two groups.

Tables 3, 4 and 5 include information about the individual patients. Certain cases are reported in more detail below because they illustrate points that are pertinent to the evaluation of the problem of L-glutamic acid and ammonia metabolism.

TABLE 3. *Effect of Treatment with L-Glutamic Acid in Acute Spontaneous Encephalopathy.*

Patient	Age	Sex	Diagnosis	Clinical Status	Initial Blood Ammonia Level	Therapy with L-Glutamic Acid (Sodium Salt)	Course & Outcome
	yr.				*microgm./ 100 cc.*		
C.H.	26	M	Portal cirrhosis (decompensated); ulcerative colitis.	Stupor progressing to coma	263	25 gm. intravenously daily for 6 days	During each infusion of glutamate ammonia level fell precipitously but rose again to pretreatment levels within few hours of cessation of infusion; transient clinical improvement; patient died in coma (Fig. 1).
R.I.	51	M	Portal cirrhosis (decompensated)	Patient drowsy & confused; steady downhill course.	359	25 gm. intravenously daily for 2 days	Transient fall in ammonia levels during infusion but over-all picture that of steady progression to coma & death with rising ammonia levels
M.K.	55	F	Hemachromatosis; esophageal varices.	Patient stuporous	223	25 gm. intravenously daily for 2 days	Coma & death; ammonia levels rose steadily except for transient fall during infusions.
M.L.	39	F	Acute yellow atrophy (homologous serum jaundice)	Patient stuporous	293	25 gm. intravenously	No change in ammonia level or clinical status during infusion; within few hours level rose to 513 microgm. per 100 cc., & patient died in coma.
B.P.	24	F	Acute yellow atrophy (homologous serum jaundice)	Maniacal state progressing to stupor & coma	232	25 gm. intravenously	During infusion ammonia level fell to 74 microgm. per 100 cc., & coma lightened perceptibly; within 24 hours level had risen to 383 microgm. per 100 cc., & patient died in coma.
E.P.	59	F	Portal cirrhosis, esophageal varices & repeated hematemesis	Patient became comatose 3 days after portacaval shunt	239	50 gm. intravenously in 48 hr.	Transient fall in ammonia levels during infusion; patient died in coma 5 days after operation.

Case Reports

Case 1. C.H. (M.G.H. 767827), a 26-year-old graduate student with known ulcerative colitis and postnecrotic cirrhosis of the liver, entered the hospital in an advanced stage of decompensation of the liver. Clinical jaundice was apparent, and he was in a state of confusion and disorientation, which rapidly progressed to deep stupor. Since there was no apparent exogenous factor involved in the "hepatic coma," this was classified as a case of acute spontaneous encephalopathy. A portion of the hospital course and treatment is shown in Figure 1. Despite a fall in blood ammonia levels during infusions of sodium glutamate there was only transient improvement, and the hospital course was one of progressive hepatic decompensation terminating in death.

This case was fairly typical of the other cases of acute spontaneous encephalopathy since only transient clinical benefit was achieved by the use of L-glutamic acid. The details are of interest in that frequent measurements of blood ammonia levels over

a space of several hours demonstrated a fall in ammonia during treatment with sodium glutamate, but deep coma. The ammonia level on the day after entry was 225 microgm. per 100 cc. Sodium glutamate infusions were begun and continued at a dosage of 25 gm. daily for 3 days.

TABLE 4. *Effect of Treatment with L-Glutamic Acid in Acute Exogenous Encephalopathy.*

PATIENT	AGE	SEX	DIAGNOSIS	PRECIPITATING FACTOR	CLINICAL STATUS	INITIAL BLOOD AMMONIA LEVEL	THERAPY WITH L-GLUTAMIC ACID (SODIUM SALT)	COURSE & OUTCOME
	yr.					*microgm./ 100 cc.*		
E.B.	73	F	Portal cirrhosis	Bleeding from esophageal varices	Deep coma	735	25 gm. intravenously daily for 2 days	Ammonia level fell steadily to 103 microgm. per 100 cc., & coma lightened perceptibly; on 6th day exsanguination occurred suddenly (Fig. 4).
G.B.	60	M	Portal cirrhosis*	Bleeding into gastrointestinal tract postoperatively	Patient stuporous	191	25 gm. intravenously	Ammonia level fell to 99 microgm. per 100 cc., & patient became responsive but died 2 wk. later after further hemorrhage
H.G.	65	F	Portal cirrhosis; ascites.	3 gm. of ammonium chloride daily for 5 days	Deep stupor	253	25 gm. intravenously	Ammonia level fell to 150 microgm. per 100 cc., & patient became responsive but died 2 days later from cerebrovascular accident.
J.L.	63	M	Portal cirrhosis; diabetes mellitus.	Bleeding from esophageal varices	Patient disoriented & confused	196	25 gm. intravenously daily for 3 days	Temporary improvement but bleeding continued; ammonia level rose to 476 microgm. per 100 cc., & patient died in coma.
M.I.	67	M	Polycythemia vera; splenic-vein thrombosis; esophageal varices.	Upper gastrointestinal hemorrhage	Patient stuporous	250	25 gm. intravenously	Ammonia level fell to 167 microgm. per 100 cc.; patient died within few hours of massive infarction of small bowel.
A.M.	63	M	Portal cirrhosis; ascites.	Ammonium chloride used as diuretic	Patient drowsy & confused	188	(See Fig. 5)	Improvement on glutamic acid by mouth (Fig. 5)
M.M.	60	F	Portal cirrhosis; esophageal varices.	Upper gastrointestinal bleeding	Patient stuporous	225	25 gm. intravenously daily for 2 days	Patient became alert & oriented, & ammonia level fell to 69 microgm. per 100 cc.; no further immediate bleeding.
M.M.	52	F	Portal cirrhosis; esophageal varices.	Upper gastrointestinal bleeding for 2 days before entry	Patient stuporous	252	25 gm. intravenously daily for 3 days	Bleeding controlled with Sengstaken tube; ammonia fell to 106 microgm. per 100 cc., & patient returned to normal mental status (Fig. 2).
C.M.	46	M	Portal cirrhosis; esophageal varices.	Upper gastrointestinal bleeding	Patient stuporous	299	25 gm. intravenously	Ammonia level fell to 255 microgm. per 100 cc., but exsanguination occurred
E.M.	51	M	Portal cirrhosis (decompensated)	Upper gastrointestinal bleeding	Patient stuporous	162	25 gm. intravenously	Ammonia level fell to 120 microgm. per 100 cc., but patient did not improve & died within 24 hr.
W.M.	64	M	Portal cirrhosis†	Recurrent bleeding 3 wk. after ligation	Patient stuporous	240	25 gm. intravenously daily for 3 days	Ammonia level fell to 99 microgm. per 100 cc., & patient became responsive but died in coma after further hemorrhage, with ammonia level of 462 microgm. per 100 cc.
H.O.	40	M	Portal cirrhosis†	Recurrent hemorrhage after ligation	Deep coma	311	50 gm. intravenously	Ammonia level fell to 122 microgm. per 100 cc. after infusion but rose again to 318 microgm. within 12 hr.; patient died in coma.
N.S.	63	M	Portal cirrhosis‡	Hemorrhage from varices in colon requiring sigmoid resection	Patient very drowsy, confused & disoriented	250	25 gm. intravenously daily for 2 days	Ammonia level fell steadily to 97 microgm. per 100 cc., & 3 days after therapy started, clinical status normal (Fig. 3)
S.T.	47	F	Portal cirrhosis; esophageal varices.	Massive upper gastrointestinal hemorrhage	Deep coma	518	50 gm. intravenously in 24 hr.	Ammonia level fell to 115 microgm. per 100 cc., but patient died within 48 hr. of entry without clinical improvement

*Splenorenal shunt on 11/27/54.
†Esophageal varices ligated.
‡Splenorenal shunt 2 yr. previously.

a return to pretreatment levels occurred shortly after the conclusion of the infusion.

CASE 2. M.M. (M.G.H. 823575), a 52-year-old woman with known, well compensated cirrhosis of the liver, was admitted to the hospital after a massive hematemesis. On admission she was mildly confused and disoriented. The bleeding from esophageal varices was controlled by a Sengstaken tube, but the neurologic state progressed rapidly to Within 48 hours the ammonia level had fallen to within the normal range, and the coma had lightened perceptibly. These events are charted diagrammatically in Figure 2. The mental status improved steadily and within 1 week was entirely normal. The subsequent course, which ultimately terminated in recurrent hemorrhage and death, is not pertinent to the present problem.

This is an example of what appears to have been a favorable effect of L-glutamic acid on elevated am-

monia levels associated with an exogenous encephalopathy. In this case the specific nitrogenous factor was the introduction of large amounts of blood into the gastrointestinal tract from the bleeding esophageal varices.

CASE 3. N.S. (M.G.H. 180376), a 63-year-old man with well compensated cirrhosis of the liver, had had a splenorenal shunt performed 2 years previously because of recurrent bleeding from esophageal varices. He had been entirely well until the present admission, which was precipitated by sudden massive rectal bleeding. This hemorrhage was severe enough to require laparotomy and resection of the sigmoid colon because of large, tortuous, bleeding veins in this segment of bowel. He appeared well on the day after operation, but within a few hours the mental status became clouded and progressed rapidly to a deep stupor. The ammonia level was 250 microgm. per 100 cc. An infusion of sodium glutamate was started and given at the rate of 25 gm. daily for 2 days. At the end of the 2d day the blood ammonia level had fallen to below 100 microgm. per 100 cc., and it remained almost at normal limits thereafter (Fig. 3). Concomitantly, there was a steady improvement in the neurologic status, which was classified as normal by the end of the 4th postoperative day. He convalesced uneventfully and was discharged.

This case represents another example of the effect of bleeding into the gastrointestinal tract as a cause of ammonia intoxication, which is remediable provided the exogenous factor can be controlled. Again, it appears that L-glutamic acid was an effective therapeutic agent. This represents a rare case of hemorrhage from varices in the lower gastrointestinal tract.

CASE 4. E.B. (M.G.H. 768591), a 73-year-old woman with known cirrhosis of the liver and esophageal varices, was admitted to the hospital in deep coma after a massive upper gastrointestinal hemorrhage. The initial ammonia level of 735 microgm. per 100 cc. was the highest level measured in man in this hospital. A constant slow infusion of sodium glutamate was started after the hemorrhage had been controlled by a Sengstaken tube. The infusion was continued for 48 hours, with a total administered dose of 50 gm. of sodium glutamate. At the end of this time the ammonia level had fallen to and stabilized at approximately 100 microgm. per 100 cc. The depth of coma lightened perceptibly, and during the next 5 days the patient became more responsive although still somewhat stuporous, confused and disoriented. The Sengstaken tube had been withdrawn, and at this point she had a sudden exsanguinating hemorrhage and died within 1 hour. These events are charted in Figure 4.

This case represents another example of exogenous encephalopathy subsequent to massive upper gastrointestinal bleeding. In this case a sudden dramatic fall in blood ammonia levels was associated with the

TABLE 5. *Effect of Treatment with L-Glutamic Acid in Chronic Encephalopathy.*

PATIENT	AGE	SEX	DIAGNOSIS	CLINICAL STATUS & COURSE BEFORE THERAPY	INITIAL BLOOD AMMONIA LEVEL	THERAPY WITH L-GLUTAMIC ACID	COURSE & OUTCOME
	yr.				*microgm./ 100 cc.*		
J.B.	58	M	Cancer of pancreas*	Recurrent episodes of confusion & stupor	182	25 gm. daily (by mouth)	On therapy mental status remained normal & ammonia level fell below 100 microgm. per 100 cc.; symptoms returned whenever glutamic acid omitted for few days (Fig. 7).
E.D.	63	F	Portal cirrhosis	Recurrent episodes of confusion 3 mo. before entry	317	25 gm. daily (by mouth)	Within 1 wk. mental status normal, & ammonia levels below 140 microgm. per 100 cc.; patient discharged on glutamic acid.
J.F.	45	M	Portal cirrhosis†	Chronic mild confusion & recurrent episodes of stupor	321	(See Fig. 6)	Mental status normal, & ammonia levels much lower on glutamic acid (Fig. 6)
F.F.	63	M	Portal cirrhosis‡	Chronic confused state & recurrent episodes of stupor	410	25-50 gm. daily (by mouth)	Except during 1 infusion of sodium glutamate ammonia levels never fell below 200 microgm. per 100 cc.; no apparent improvement in mental status.
H.G.	52	F	Portal cirrhosis	Chronic confused state for 1 yr.	336	25 gm. daily (by mouth)	On glutamic acid striking improvement in mental status; ammonia levels ranged between 100 & 200 microgm. per 100 cc.
M.S.	43	F	Portal cirrhosis (with jaundice & ascites)	Patient drowsy & confused	290	25 gm. of sodium salt intravenously for 2 days; glutamic acid, 30 gm. daily, by mouth.	Ammonia level stabilized at about 150 microgm. per 100 cc., & mental status returned to normal
E.T.	55	M	Portal cirrhosis; esophageal varices.	Chronic confused state for several wk. before admission	234	25 gm. daily (by mouth)	Mental status returned to normal within 48 hr.; subsequent ammonia levels remained below 150 microgm. per 100 cc.; patient died several mo. later in "liver failure."
H.W.	64	M	Portal cirrhosis§	Increasing confusion & drowsiness, with recurrent episodes of stupor	217	30 gm. daily (by mouth)	Some improvement on therapy, but patient never returned completely to normal

*Resection of portal vein with Eck fistula.
†Splenorenal shunt 3 yr. previously.
‡Portacaval shunt 4 yr. previously.
§Portacaval shunt 4 mo. before this admission.

infusion of sodium glutamate. The improvement in cortical function proceeded at a steady but much slower pace.

CASE 5. A.M. (M.G.H. 841312), a 63-year-old man with known cirrhosis of the liver, entered the hospital for treatment of intractable ascites. Ammonium chloride was

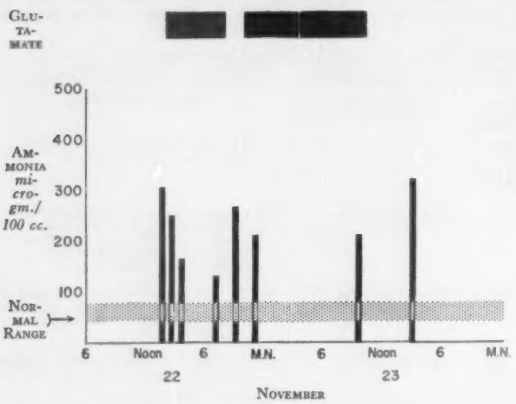

FIGURE 1. *Effect of L-Glutamic Acid on Blood Ammonia Levels in Case 1.*

This patient had postnecrotic cirrhosis and ulcerative colitis as well as acute spontaneous encephalopathy.

started as a diuretic agent, and within 24 hours he became confused, disoriented and stuporous, with a blood ammonia level of almost 200 microgm. per 100 cc. At this point ammonium chloride was discontinued, and L-glutamic acid given orally in a dosage of 25 gm. daily for 3 days, at the end of which both the ammonia level and the mental status were normal. Two weeks later ammonium chloride was given again and again was followed by a rapid deterioration in the neurologic status, with a concurrent elevation in the blood ammonia level to 200 microgm. per 100 cc. Again, ammonium chloride was withdrawn, and glutamic acid therapy started, with a rapid improvement in the mental status. At this point ammonium chloride therapy was reinstated, but L-glutamic acid was continued. This time a satisfactory diuresis was achieved, no mental changes occurred, and only a slight elevation in the blood ammonia level was noted. The relation between the use of ammonium chloride without and with glutamic acid and the blood ammonia levels and neurologic status is demonstrated in Figure 5.

In this case of exogenous encephalopathy the precipitating factor was the oral administration of ammonium chloride. It appears that L-glutamic acid was effective not only in correcting the disturbances in ammonia metabolism and cortical function induced by ammonium chloride but also in preventing these disturbances if administered simultaneously with ammonium chloride.

CASE 6. J.F. (M.G.H. 761945), a 47-year-old man, had had a splenorenal shunt performed 3 years previously for portal hypertension and bleeding esophageal varices. The full details in this case are not pertinent, but when he first came under specific observation he was in a state of chronic mental confusion, with occasional severe exacerbations. Measurements of peripheral blood ammonia ranged consistently between 200 and 250 microgm. per 100 cc. After a period of observation L-glutamic acid was started by mouth in divided doses totaling 25 gm. daily. By the end of 1 month the mental status was dramatically improved, and he could be classified as entirely normal for the 1st time in over 2 years. At the same time the blood ammonia level fell to a level just above that of normal controls.

The course under study and treatment is shown in Figure 6. Over the next 14 months L-glutamic acid therapy was repeatedly withdrawn, and on each occasion mental confusion recurred and blood ammonia levels rose. When L-glutamic acid was reinstituted, both biochemical and clinical improvement was apparent. Over this entire period of 14 months the patient was on a controlled diet permitting only 60 gm. of protein daily.

This case represents an example of chronic encephalopathy. The administration of L-glutamic acid on a number of occasions was accompanied by

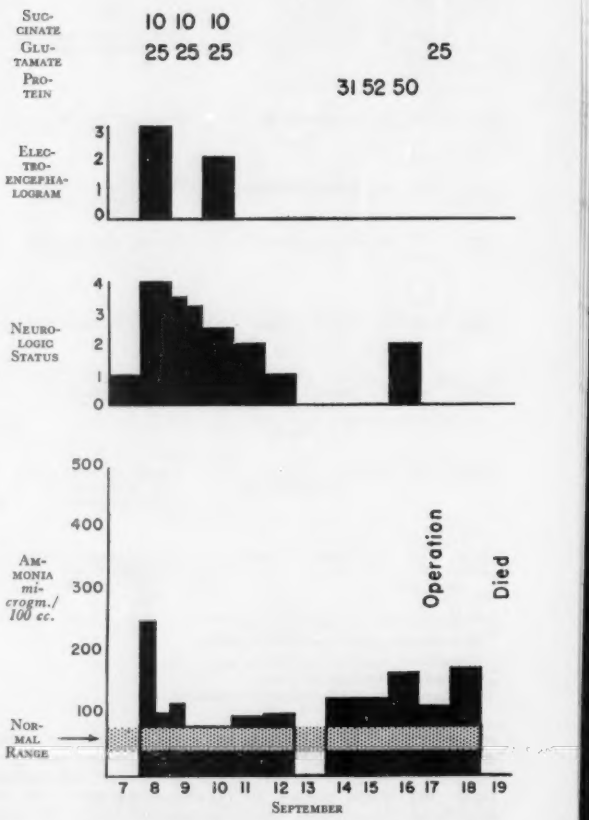

FIGURE 2. *Effect of L-Glutamic Acid on Acute Exogenous Encephalopathy in Case 2.*

This patient had portal cirrhosis and bleeding esophageal varices.

a return to normal mental status and by a fall in blood ammonia levels. As shown in Figure 6, this pattern was so consistent that it could hardly be explained by coincidence.

CASE 7. J.B. (M.G.H. 799394) was a 58-year-old man in whom an Eck fistula had been constructed after resection of the portal vein for cancer of the pancreas. Even on a diet with protein restricted to 40 gm. daily, he remained

in a state of chronic confusion and disorientation. Blood ammonia levels ranged between 175 and 200 microgm. per 100 cc. The administration of L-glutamic acid was attended by a fall in ammonia levels and by a restoration of cortical function to normal (Fig. 7). He subsequently died of recurrent cancer.

This case of chronic encephalopathy differs from the preceding case in that the Eck fistula was constructed in the presence of a normal liver. Previously reported studies on a similar case[14] had stimulated interest in this laboratory in the problems of ammonia metabolism in man.

Discussion

The clinical and biochemical data presented above suggest that L-glutamic acid frequently has a definite effect on the neurologic symptoms associated with disease of the liver or portal circulation and on the concomitant disturbance in ammonia metabolism.

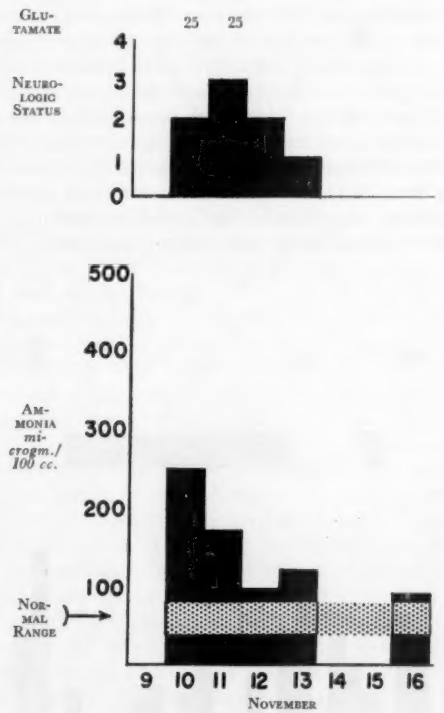

Figure 3. *Effect of L-Glutamic Acid on Acute Exogenous Encephalopathy in Case 3.*
This patient had portal cirrhosis with bleeding sigmoidal varices. (The electroencephalogram was not recorded.)

The effect of this amino acid becomes more apparent if these hepatic encephalopathies are divided into the three main classifications outlined above: acute spontaneous encephalopathy; acute exogenous encephalopathy; and chronic encephalopathy.

The first group comprises patients who enter the hospital with a decompensated liver and with the appearance of neurologic symptoms that in general progress inexorably to coma and death. In the small group reported in this series the use of L-glutamic acid had little or no apparent clinical effect on the

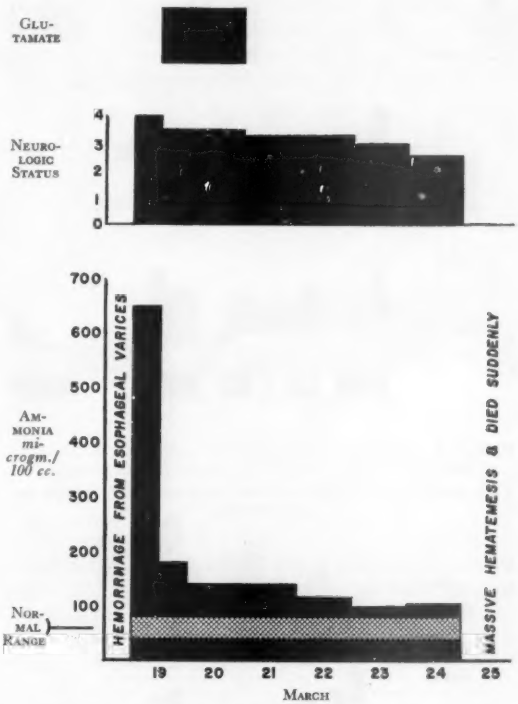

Figure 4. *Effect of L-Glutamic Acid on Acute Exogenous Encephalopathy in Case 4.*
This patient had portal cirrhosis and bleeding esophageal varices.

progress of the disease. If the ammonia levels were measured frequently and followed carefully, however, there was in most cases evidence that a temporary fall occurred during administration of L-glutamic acid but that it was followed by a rise to pretreatment levels as soon as the immediate administration of the drug was discontinued. These observations should not be surprising or discouraging. If an organ as important and with as many functions in carbohydrate, protein and fat metabolism as the liver is damaged to the extent that it begins to fail one would expect to find — and it is becoming increasingly apparent that one will find — innumerable biochemical disturbances associated with this inadequate hepatic function. The disturbances in ammonia metabolism (which have been previously described and discussed in detail) are only one of the many metabolic derangements that occur in the presence of the failing liver. An attempt to restore the patient to normal health by a therapy designed only to control high

levels of ammonia in the blood is obviously doomed to failure for two main reasons: the problem of ammonia intoxication is but one of the many facets associated with decompensation of the liver and varies in importance from case to case; and, in any clinical case that demonstrates spontaneous hepatic decompensation, one would not expect to control a biochemical abnormality such as this more than temporarily unless one could visualize a restoration of relatively normal hepatic function. We emphasize again that any concept of ammonia intoxication as the *only* biochemical abnormality associated with the decompensated liver represents a false approach to this entity.

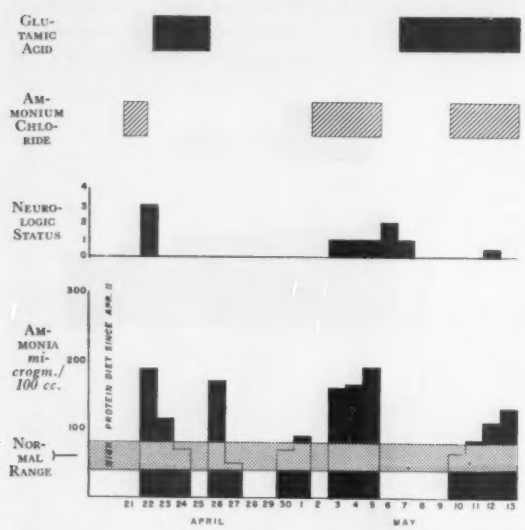

FIGURE 5. *Effect of Ammonium Chloride and L-Glutamic Acid, Given Singly and in Combination, in Case 5. This patient had portal cirrhosis and acute exogenous encephalopathy.*

In the condition referred to above as acute exogenous encephalopathy a different situation exists. All these patients were in a stage that could be reasonably described as compensated disease of the liver or portal circulation until there was a sudden addition of a nitrogenous load in the gastrointestinal tract. In other words, although most of these patients had evidence of some disturbances of hepatic function by the standard liver-function tests, from the clinical point of view they were in reasonably good health and without neurologic symptoms until a sudden change occurred that precipitated the typical encephalopathy of liver disease. These factors might include a high-protein intake, the use of ammonium chloride or urea as a diuretic or the sudden flooding of the gastrointestinal tract with blood, usually from esophageal varices. All these exogenous factors have a common denominator in the large nitrogenous pool that is introduced into the gastrointestinal tract and may then be split to more basic compounds and in turn form ammonia by the action of bacterial enzymes such as amino acid oxidase and urease. Because of the presence of a portal-bed block or a surgically constructed portacaval shunt, this absorbed

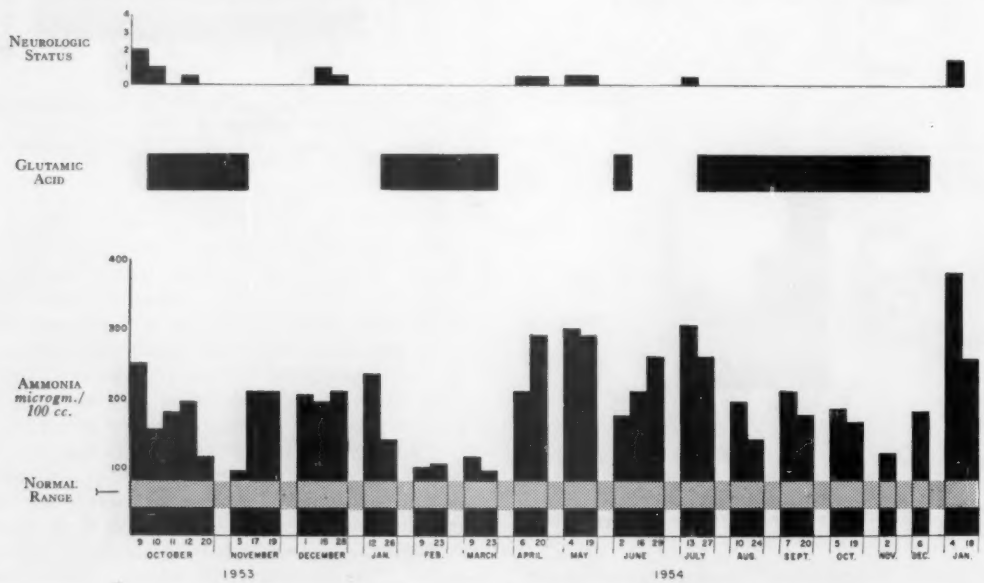

FIGURE 6. *Effect of L-Glutamic Acid on Chronic Encephalopathy in Case 6. This patient had had a splenorenal shunt for portal hypertension.*

ammonia will then bypass the liver and reach high concentrations in the peripheral blood. In this type of problem one might reasonably expect that a substance that could lower the blood ammonia might well result in a permanent improvement, provided the exogenous factor was not continued. This expectation has been borne out, as evidenced by the results already described.

In the third group of cases, classified as chronic encephalopathy, a peculiar situation exists. In these cases an abnormal but relatively stable situation seems to have been reached in which a high but also fairly stable ammonia level in the peripheral blood exists, and the patient presents definite but mild neurologic symptoms. Instead of showing the progressive and almost inexorable course of the spontaneous encephalopathies, or the acute exacerbations evidenced by the exogenous encephalopathies, these patients remain for days, weeks, or even months in a state of mild fluctuation, with no evidence of improvement or regression. Most of the patients in this study were on a controlled and relatively low-protein intake ranging between 50 and 70 gm. daily. This program often resulted in some improvement in clinical status, but the restriction of nitrogenous intake alone was not sufficient to restore them to normal. In this particular group, again, one might expect a substance that would control the ammonia level in the peripheral blood to effect a permanent improvement, and such improvement occurred in the majority of these cases. There is no question that the addition of glutamic acid by mouth has proved to be effective both in restoring normal mental status and in achieving a fall in the blood ammonia while these patients were taking the drug. This relation is particularly apparent in the patient whose clinical course and biochemical studies over a period of sixteen months are presented in Figure 6. It seems most unlikely that coincidence alone accounted for the improvement both in ammonia levels and in clinical status that consistently occurred on so many occasions with the addition of glutamic acid to the therapeutic regimen and for the regression that repeatedly occurred when glutamic acid was withdrawn. It is obvious from the data that all these patients did not respond equally to glutamic acid, and 1 case out of the 8 was classified as a failure of treatment; the exact reasons for the ineffectiveness of this therapy in this case are not apparent from these data.

The observations reported above are not unique. Eiseman[41] observed in his patients the same clinical differences that led us to distinguish between "spontaneous" and "exogenous" encephalopathy. The fact that L-glutamic acid has not been invariably effective has also been noted by Webster and Davidson.[42] These investigators, studying primarily the "spontaneous" type of hepatic coma, found many cases with no clinical improvement. They also found that increasing the daily dose of L-glutamic acid to 100 gm. or more invariably produced a distinct although frequently only a transient fall in blood ammonia levels.

It is hoped that these and similar studies on L-glutamic acid and ammonia metabolism will help to clarify some of the existing confusion. Two facts seem apparent: ammonia intoxication is a specific entity in "exogenous" encephalopathy, but disturbances in ammonia metabolism represent only one facet of the complex biochemical changes associated with the decompensated liver ("spontaneous" encephalopathy); and L-glutamic acid has a definite role in the treatment of encephalopathy associated with disorders of the liver and portal circulation but obviously cannot be expected to restore or replace the failing liver.

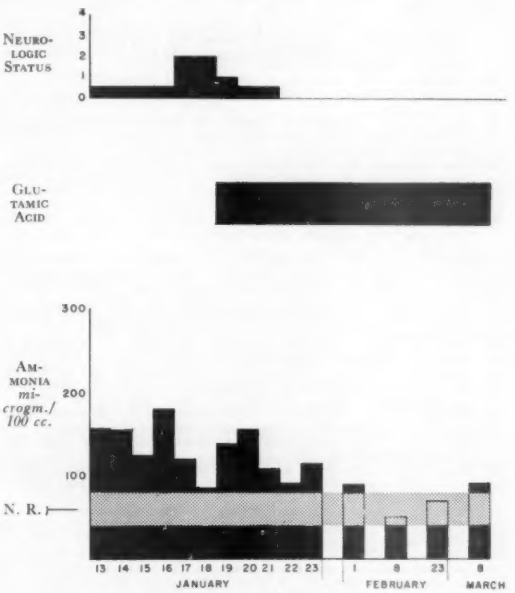

FIGURE 7. *Effect of L-Glutamic Acid on the Subsequent Chronic Encephalopathy in Case 7 (N.R. = Normal Range). This patient had had a portacaval shunt after resection of the portal vein for cancer of the pancreas.*

SUMMARY AND CONCLUSIONS

The effect of L-glutamic acid on 28 patients with "hepatic coma" is described.

These cases have been divided into three groups: "spontaneous," "exogenous" and "chronic" encephalopathy. In the "exogenous" and "chronic" groups ammonia intoxication has been the predominant feature and L-glutamic acid has proved to be an effective adjunct to treatment. The patients with "spontaneous" encephalopathy represent cases of true hepatic decompensation; in this group the disorder of ammonia metabolism is only one of many biochemical defects, and L-glutamic acid has proved to have only transient effects.

If the term "hepatic coma" is to be retained, it would be well to distinguish between "spontaneous hepatic coma," which includes all the complex known and unknown disorders of the failing liver, and "exogenous hepatic coma," which refers primarily to the syndrome of ammonia intoxication.

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THE ELECTROENCEPHALOGRAM IN RETROLENTAL FIBROPLASIA*

E. L. Gibbs,† Alberto Fois, M.D.,‡ and Frederic A. Gibbs, M.D.§

CHICAGO

RETROLENTAL fibroplasia[1] is characterized by blindness due to the formation of an opaque membrane behind the lens. It usually occurs in infants born prematurely with a birth weight of about 1.3 kg. (3 pounds) or less. The number of cases has greatly increased in the last ten years, and the disease has become, in some regions, a major cause of blindness among preschool children.[2] It has been described as a primary disease of the retinal blood vessels, which become tortuous and dilated and proliferate. The process commonly goes on to neovascularization, detachment of the retina and the formation of a retinal membrane behind the lens.

Campbell[3] was the first to collect evidence that the breathing of a high-oxygen atmosphere by the premature infant might be a cause of retrolental fibroplasia. Experiments by Gyllensten and Hellström[4] with newborn mice showed that intermittent exposure to 100 per cent oxygen for one to three weeks produced an ocular disease similar to retrolental fibroplasia of premature infants. Patz, Hoeck and De La Cruz[5] reported that the incidence and grade of retrolental fibroplasia were positively related to the oxygen

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level in the infant's incubator. Some cases of retrolental fibroplasia have been reported in which no oxygen was added to the respired air,[6] but Patz et al.[5] point out that a normal atmosphere consisting of 20 per cent oxygen provides the infant with more oxygen than it receives in utero, and thus the oxygen level

TABLE 1. *Clinical Status of 51 Cases of Retrolental Fibroplasia.*

STATUS	NO. OF CASES	PERCENTAGES
Intelligence:		
Normal	18	35
Retarded	33	65
Total	51	
Average		100
Clinical seizures:		
Absent	37	73
Present	14	27
Total	51	
Average		100
Cerebral palsy:		
Absent	46	90
Present	5	10
Total	51	
Average		100

of room air may be abnormally high for a premature infant. Szewczyk[7] has suggested that sudden anoxia produced by abrupt removal of the premature infant from a high-oxygen atmosphere is an important etiologic factor, but this is questioned by Patz and his

TABLE 2. *Electroencephalographic Findings during Waking and Sleeping States.*

OCCURRENCE OF SEIZURE ACTIVITY	NO. OF CASES*	PERCENTAGES*
Awake	17	33
Asleep	38	75

*Figures nonexclusive so that when totaled they do not add up to number of cases in series or 100 per cent.

associates.[5] Lanman, Guy and Dancis[8] found that retrolental fibroplasia was present in a group of premature infants treated with high oxygen but absent in a group treated with low oxygen or no oxygen therapy. They concluded that the disease is directly related to excessive administration of oxygen and can be controlled by limitation of this therapy.

The association of retrolental fibroplasia with mental retardation has been a subject of controversy since Krause[10] named the disease "encephalophthalmic dysplasia." Long-term study of patients with this condition has led Krause to the conclusion that in many cases the mental retardation is more apparent than real and that it is commonly the result of limited opportunities to learn,[11] but in some cases, particularly those in which seizures or motor defects are present, the mental retardation is due to true cerebral dysfunction.

A study by Jim and Krause[12] of the electroencephalogram in retrolental fibroplasia failed to provide

TABLE 3. *Abnormalities Found with Patient Awake or Asleep.*

ELECTROENCEPHALOGRAPHIC CLASSIFICATION	NO. OF CASES		PERCENTAGE	
Occipital spike focus	29		55	
Occipital spike focus & other seizure activity	8	37	17	72
Hypsarrhythmia		2		4
14 & 6 per second positive spikes		1		2
Normal		11		22
Total		51		
Average				100

significant findings. However, others have shown a correlation between eye disorders in children and electroencephalographic abnormality — for example, occipital abnormalities are commonly associated with eye defects and a history of premature birth[13] and eye disorders[14] and strabismus[15] correlate with electroencephalographic abnormalities in the occipital areas. It seemed desirable to reconsider the electroencephalogram in retrolental fibroplasia with recordings made in both waking and sleeping states.

MATERIAL AND METHOD

The total case material on which the present study is based consisted of 51 patients under sixteen years

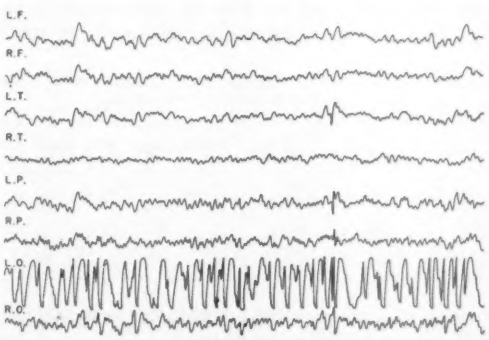

FIGURE 1. *Slow-Wave Focus and Spike Discharges in the Left Occipital Area in a Four-Year-Old Mentally Retarded Boy with Retrolental Fibroplasia.*

of age. Twenty-five patients were from a university clinic; 17 were from a large state institution for retarded children; and 9 were referred by physicians in private practice. Patients from the university clinic and those referred from private practitioners were examined by clinical psychologists and judged to be

mentally retarded when the I.Q. was below 70. Allowance was made for the handicap of blindness, and patients with borderline cases were given the benefit of the doubt and classified as nonretarded. All the institutionalized patients had been studied clinically before admission and declared committable because of severe mental retardation. The frequency of mental retardation, epileptic seizures and cerebral palsy in this group is shown in Table 1.

Routine recordings were made with a Grass 8-channel electroencephalograph. Solder-disk electrodes were fastened with collodion to different areas of the scalp. Electrodes were applied to the frontal, parietal, temporal and occipital areas. Recordings were monopolar; one ear lobe or interconnected ear lobes were the most commonly employed reference points. In all cases except 1, recordings were made in both waking and sleeping states.

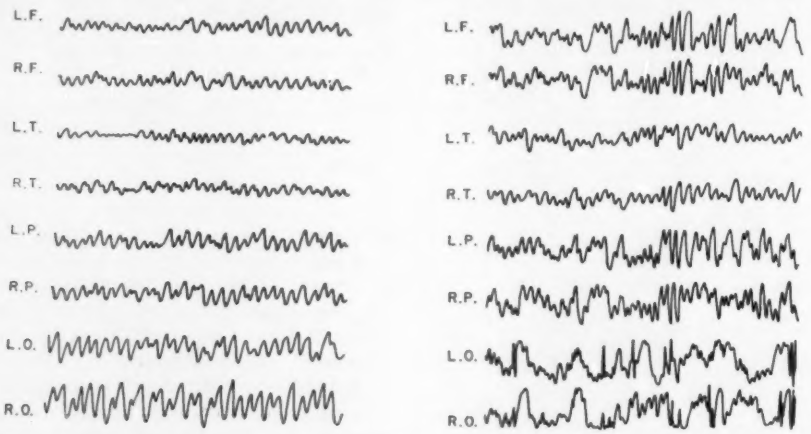

FIGURE 2. *Electroencephalogram of a Twenty-seven-Month-Old Boy of Normal Intelligence with Retrolental Fibroplasia Who Was Blind in the Right Eye but Had Light Perception in the Left.*
The record, which is normal with the patient awake, shows high-voltage spikes in both occipital areas when he is asleep.

TABLE 4. *Relation between Age and Electroencephalogram in 51 Cases of Retrolental Fibroplasia.*

AGE	NO. OF PATIENTS	NORMAL RECORD	OCCIPITAL SPIKE FOCUS	OTHER TYPES OF SEIZURE ACTIVITY
yr.		%	%	%
0-2	20	50	35	15
3-14	31	3	74	23

RESULTS

In retrolental fibroplasia (as in other conditions in which epilepsy is present[13]) the electroencephalographic recording revealed more seizure activity during sleep than in the waking state (Table 2). When electroencephalograms were classified without relation to whether the abnormalities were present in waking or sleeping states (Table 3) an occipital spike focus was the commonest abnormality (Fig. 1 and 2), occurring in 72 per cent of the entire series. All patients with a history of clinical seizures, and 70 per cent of patients without such a history had seizure activity of some type. The frequency of seizure discharges was different in different age groups. Only 35 per cent of children under three years of age had occipital spike foci, whereas 74 per cent of those who were three years of age or older had occipital spike foci. Other types of seizure activity were also commoner in older children than in the younger (Table 4).

One child with retrolental fibroplasia had minimal focal abnormalities and was considered to be within normal limits at the age of eight months, but at twelve months the patient had a high-voltage spike focus in both occipital areas (Fig. 3 and 4).

DISCUSSION

In retrolental fibroplasia prematurity is a factor of primary etiologic importance.[1] The vulnerability of different parts of the brain varies with age,[16] and it is possible that premature tissue is particularly sensitive to high-oxygen tension, and also possible that the occipital lobes are especially vulnerable to this factor.[13] A number of important enzymes containing S-H groups are disrupted by high-oxygen tension,[17] and as a consequence glucose oxidation may cease at the pyruvic acid level, with a resultant histotoxic anoxia.[12] Thus, high-oxygen tension may produce a reduction in oxygen utilization and a state comparable to that occurring with oxygen lack.

The study of human epilepsy[13] and also animal studies by Grossman[18] have shown that different types of electroencephalographic abnormality tend to appear at different ages. The commonest focus in human infants, regardless of the nature of the pathologic agent, is an occipital focus.[13] Occipital foci are

common in premature infants,[13] but in such infants eye defects of some type are also common; the frequency of occipital-lobe disorder in premature infants with normal vision has not been determined.

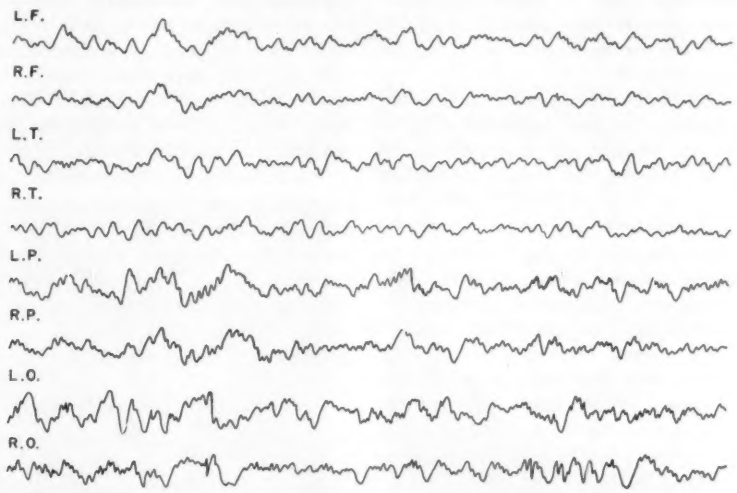

FIGURE 3. *Electroencephalogram of an Eight-Month-Old Boy with Retrolental Fibroplasia Who Showed Slow Development but Was Not Obviously Retarded.*
The record is within normal limits, with minimal low-voltage, sharp spikes in the occipital areas.

With increasing age occipital-lobe foci tend to disappear or to migrate forward into the midtemporal region.[19,20] Therefore, if the present group of patients were studied at a later age occipital-lobe foci would probably be rarer, and midtemporal-lobe foci more frequent. Long-term follow-up studies have shown that this disappearance and shifting of foci is not peculiar to any particular kind of epilepsy. Even in cases in which the structural lesion is restricted to the occipital region (for example, in an infant with a gunshot wound in the occipital lobe) the seizure activity that is at first present in the occipital area may disappear and may be replaced by seizure activity in the midtemporal area.

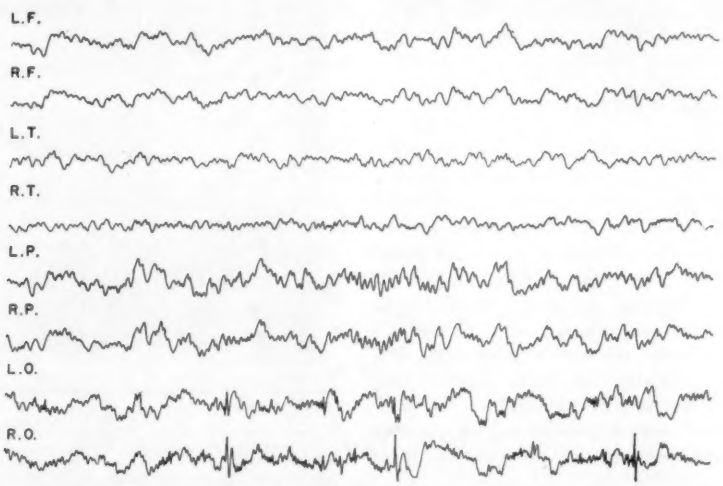

FIGURE 4. *Electroencephalogram of the Patient Referred to in Figure 3 at the Age of Twelve Months, Showing a Focus of High-Voltage Spike Discharges in both Occipital Areas that is Maximal on the Right.*

As indicated in the present material there is a high correlation between seizure activity and clinical seizures. However, epilepsy may be subclinical; seizure activity can be present without clinical manifestations. Forty per cent of children with cerebral palsy have subclinical epilepsy.[21]

That the electroencephalographic abnormality and the eye defects are direct consequences of the same

primary disturbance — namely, excessive oxygen — seems a reasonable assumption. However, overexposure of the immature brain to visual stimulation might produce the occipital-lobe disorder, but the eye disorder itself is not prevented by covering of the eyes with an opaque shield.[19]

Another means by which the eye defect may result in occipital-lobe disorder has been suggested to us by Vonderahe.[22] He has pointed out that one of the earliest methods of studying the sensory projection areas in the brain was that of Von Gudden, who showed that when a peripheral sense organ is removed in a newborn animal, the primary and secondary projection areas degenerate or fail to develop. Von Gudden and his followers employed this method for anatomic studies; however, the procedure was not much used after the advent of staining technics, for a stained degenerating tract was easier to see than a system that was absent. Vonderahe[22] suggests that blindness occurring in early infancy might result in dysfunction of the entire visual apparatus and that the occipital seizure discharges in children with retrolental fibroplasia might be an electroencephalographic evidence of this dysfunction. The observation of Cannon and Rosenblueth[23] that all deafferented systems tend to become hypersensitive may explain why the dysfunction takes the form of seizure discharges. However, this explanation has limitations, for in our experience blindness acquired later in life is not associated with occipital spike discharges. The causal linkages between prematurity, excessive oxygen, retrolental fibroplasia and occipital-lobe spike discharges remain to be determined.

Summary and Conclusions

In 51 cases of retrolental fibroplasia, electroencephalographic recordings were obtained in the waking and sleeping states. Although only 27 per cent of patients had some form of clinical epilepsy, seizure activity was present in 88 per cent of the entire group (in 100 per cent of those with seizures and in 70 per cent of those without seizures). The clinical history of seizures and the occurrence of mental retardation suggested brain disorder in some cases, but the present study indicates that brain disorder may occur in cases of retrolental fibroplasia.*

The frequency of seizure activity among younger and older children differed; 50 per cent of those under, and 97 per cent of those over three years of age had seizure activity. The commonest electroencephalographic abnormality was a focus of spike-seizure activity in one or both occipital areas. This occurred in 35 per cent of children under and 74 per cent of those over three years of age. Follow-up studies on children with occipital-lobe foci have shown that this type of focus tends to disappear with increasing age or to migrate into the midtemporal region.

The following circumstances are considered possible causes of the seizure activity in retrolental fibroplasia: trans-synaptic degenerative changes in the brain secondary to blindness in early infancy (structural evidence of such changes has been reported by Von Gudden); oxygen poisoning of the immature brain resulting from excess oxygen in the respired air; and premature photic stimulation.

*It should be observed that this series is heavily weighted in favor of mental retardation since 17 of the patients were derived from a large state institution for retarded children. The series may thus not represent an unbiased sample of the universe of patients with retrolental fibroplasia.

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THE SPONDYLITIS OF JUVENILE RHEUMATOID ARTHRITIS*

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BOSTON

SPINAL involvement in rheumatoid arthritis in children has occasionally been noted in the literature, but never emphasized or adequately described. At the Robert Breck Brigham Hospital in Boston, an institution devoted largely to rheumatic diseases, we have for some time been impressed with the large number of cases of clinical spondylitis in these children. We have therefore undertaken a survey of all cases of juvenile rheumatoid arthritis seen over the past forty years, to determine the incidence and nature of the spondylitis. The older material has not always been adequate. Thanks to the formerly popular "focus-of-infection" search many x-ray films of necks are incidentally available for study on films taken primarily to ascertain the extent of dental decay.

FIGURE 1. *Typical Posture in Spondylitis, with Forward Fixed Flexion of the Head and Neck and a Rounded Back.*

FIGURE 2. *Lateral X-Ray Film of the Neck of a Three-Year-Old Girl Whose Disease Had Begun at Two and a Half Years of Age.*

There is apophyseal damage between the third and fourth cervical vertebras, with narrowing of the joint space and roughening of the joint surfaces.

CLINICAL FINDINGS

In every case in this group spondylitis has been associated with peripheral joint disease. We have yet to see rheumatoid arthritis in a child confined to the spine. However, neck pain, stiffness and limitation of motion are sometimes present before the peripheral joints are involved.

In general, symptoms of spinal involvement appear at or soon after the onset of illness. Often, of course, the early signs and symptoms have not been recorded

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since attention was not given to this aspect of the disease. There may be pain and stiffness anywhere in the back, neck or sacroiliac regions. Limitation of motion of the neck, some fixed roundness of the thoracic spine and a flattening of the lower back develop in many of these children either early in the illness or gradually over some years. Flexion deformity of the neck is the most commonly observed deformity

FIGURE 3. *Lateral X-Ray Film of the Neck of the Same Child Three Years Later.*

There is now fusion of the apophyses between the second and third, third and fourth and fourth and fifth cervical vertebras.

There is also subluxation of the axis on the atlas. The disks, vertebras and spinous processes are underdeveloped.

and may be extreme. One of the ultimate results, as described below, is a shortened stature, owing to interference by the arthritic process with normal spine growth.

X-Ray Picture

The small joints of the spine are affected in a process that appears similar to that involving peripheral joints. There is narrowing, irregularity and often fusion of the apophyses and also of the sacroiliac joints (the frequency is mentioned below). In the areas of the spine affected the vertebral bodies are underdeveloped in height and breadth, and the intervertebral disks are likewise narrow, owing to lack of development and not to collapse. We postulate that the normal stimulus to growth of the vertebral bodies and the intervertebral spaces — that is, motion of the spine — is largely absent in the involved areas because of fusion of the spinal joints. A further factor is the immobility of the child with this illness.

An outstanding feature of the spinal arthritis in children is the lack of calcification of the paravertebral ligaments. In rare cases there is slight calcification, which is confined to the capsular ligaments but absent from the major spinal ligaments. The failure of calcification is a constant feature even with follow-up studies into adult life.

The appearance of a typical patient is shown in Figure 1, and the x-ray findings in various cases in Figures 2 to 8.

The x-ray changes described may become apparent within a few months of the onset of the disease. They have been observed to progress with amazing rapidity,

FIGURE 4. *Lateral View of the Spine of a Thirty-six-Year-Old Man Whose Arthritis Had Begun at the Age of One Year and Nine Months, Showing the Late Stages of the Disease in the Neck.*

There is extensive fusion of the posterior elements. The cervical bodies are grossly underdeveloped in all diameters, as the disks are. Slight calcification is present only in the capsular ligaments.

striking changes in 1 case being noted over a four-month period.

Total Statistics

The over-all statistical results of the study are outlined in Table 1.

Thus, in this series, and with inadequate data in some cases, 57 (80 per cent) of 71 cases of juvenile arthritis gave clinical or x-ray evidence of spinal disease. It is thus a usual finding.

Age at Onset

The average age at the first noted appearance of spondylitis was nine and six-tenths years. However,

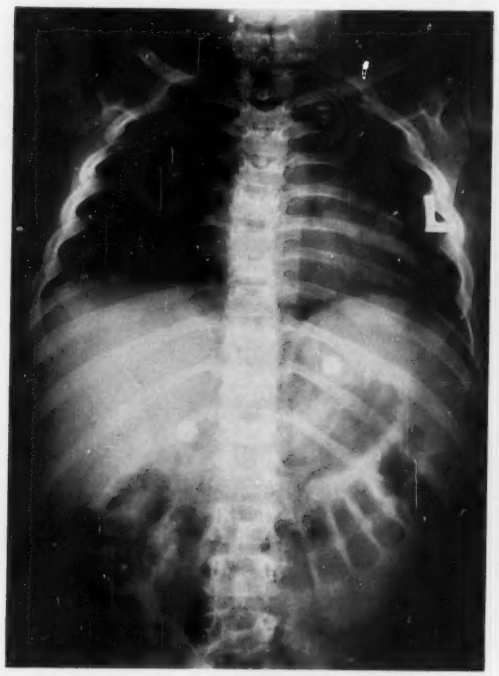

FIGURE 5. *Anteroposterior View of the Dorsal Spine of a Six-Year-Old Girl, Showing Narrowing between the Sixth and Seventh and the Seventh and Eighth Dorsal Vertebras Caused by Underdevelopment of the Disks.*

the earliest noted spondylitis was at two, and the latest at twenty-six years. It is obvious that in the case that appeared latest the disease must have begun much earlier in the spine and been overlooked. Thus, the average age at onset must be earlier than nine and six-tenths years.

TABLE 1. *Results of Study in 71 Cases of Juvenile Rheumatoid Arthritis.*

FINDING	NO. OF CASES
Clinical involvement of any part of spine	51
Clinical involvement of neck	49
Clinical involvement of spine exclusive of neck	20
Spinal involvement on either clinical or x-ray observation	57(80%)
X-ray evidence of spondylitis	49(70%)

Sex Distribution

In the entire series, there were 45 females and 26 males — in general, a similar distribution to that of the disease in adults. Of the 57 patients with spondylitis, 37 were females, and 20 males — a significant difference from the distribution in spondylitis in adults. Expressed in another way these figures show that, of 26 males in the total group, 20 (79 per cent) had spondylitis; of 45 females in the entire group, 37 (82 per cent) had spondylitis. Thus, there appears to be no evidence of a sex factor in the distribution before puberty as there is so prominently in adults.

FIGURE 6. *X-Ray Film of the Pelvis of an Eleven-Year-Old Boy at the Time of Onset of Rheumatoid Arthritis. The lumbar spine and sacroiliac articulations appear normal, though there was back pain at this time.*

X-ray evidence of involvement of individual areas of the spine is listed in Table 2.

Distinction from Congenital Failure of Segmentation

It is necessary from the radiographic point of view to distinguish between the juvenile rheumatoid type of spondylitis and congenital fusion, more properly termed "failure of segmentation." In this anomaly the failure is often at the anterior margin of the body, which is rounded. The disk is narrow, but of uniform width. The outline of the vertebral bodies and posterior elements is normal except for the failure of separation. Failure of segmentation may be complete or incomplete. In the incomplete form the posterior

halves of the bodies usually show fusion, and the anterior space is occupied by a uniformly thin disk, which is evenly rounded at the anterior margin.

Distinction from Adult Strümpell–Marie Disease

The distinguishing features between the juvenile rheumatoid type of spondylitis and the adult type (Strümpell–Marie arthritis) are that in the latter the age at onset is about eighteen years (after puberty);

Figure 7. *X-Ray Film of the Pelvis of the Same Patient at the Age of Eighteen.*
The spine is rigid. The sacroiliac articulations and the lateral articulations of the lumbar spine are completely fused.

the sacroiliac and, less often, lower dorsal joints are first affected; the costovertebral joints are also affected; and the healed end stage is that of calcified joints and ligaments. Because bone growth has occurred, the vertebral bodies and intervertebral disks are of normal height, breadth and thickness.

Summary

In a series of 71 children with juvenile rheumatoid arthritis, 57 (80 per cent) gave clinical or x-ray evidence of spinal involvement.

The areas most commonly involved were the neck and lower back.

Calcification of the paravertebral ligaments was unusual, being noted in only 2 cases in this series even with long follow-up periods.

Table 2. *Results of X-Ray Study.*

Area	Positive Examination	Negative Examination	Inadequate Data
	no. of cases	no. of cases	no. of cases
Neck	45(80%)	11	15
Dorsal spine	14	35	22
Lumbar spine	24	33	14
Sacroiliac joint	25	38	8

Females predominated in this entire series in a ratio of about 2:1. Spondylitis was about equally frequent in the two sexes.

Figure 8. *X-Ray Film of the Cervical Spine of an Asymptomatic Twenty-one-Year-Old Woman with a Negative Physical Examination but with a History of Arthritis at the Age of Two.*
There is ankylosis of the second and third cervical apophyses with a small disk between the second and third cervical vertebras; this is a residuum of juvenile rheumatoid arthritis.

In this group of children, rheumatoid spondylitis was always accompanied by peripheral joint involvement and never existed as an entity.

DISTURBANCES OF URINATION AFTER ADMINISTRATION OF CERTAIN NEWER DRUGS

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RECENT experience with a number of the newer drugs has demonstrated the need for an awareness of their potentially deleterious effects on micturition. In some cases the complications, not truly toxic in nature, were entirely due to side effects—that is, pharmacologic evidence that the drug was operating in organs and systems where these manifestations were unlooked for or undesirable. In other cases the urinary complications were mechanical in origin. The disturbances have varied in degree from mild difficulty in urination to complete urinary retention.

It is the purpose of this paper to discuss ganglionic-blocking agents, hydralazine, anticholinergic drugs, antihistamines, isonicotinic acid hydrazide, amphetamines, sulfonamides and mercurials, any of which can adversely affect micturition, and to classify these preparations according to their modes of action.

DRUGS CAUSING NEUROGENIC DISTURBANCES OF URINATION

Antihypertensive Drugs

Ganglionic-blocking agents. The medical treatment of essential hypertension has been advanced with the recent introduction of several groups of drugs. Perhaps the most potent of these are the quaternary ammonium compounds. These synthetic compounds, characterized by the presence of one or more pentavalent nitrogen groups, inhibit the transmission of impulses through all autonomic ganglions, parasympathetic as well as sympathetic. Hexamethonium and pentapyrrolidinium currently enjoy considerable vogue. Among the effects encountered with these powerful agents are micturitional disorders,[1-4] the result of parasympathetic blockage. A typical case follows.

H.H., a 55-year-old man, was first seen in July, 1952, complaining of frequent episodes of vertigo, pounding headaches associated with visual disturbances and palpitation, dyspnea and some precordial pain on exertion for several months. Examination was noteworthy in the following respects: the blood pressure was 220/140, the fundi revealed Grade 2 hypertensive retinopathy,[5] the heart was somewhat enlarged, extending to the left on roentgenography, and electrocardiography demonstrated left-axis deviation and depressed T waves in Leads 2 and 3. He was placed on a low-salt regimen with tablets of phenobarbital, 15 mg. (¼ gr.) 3 times daily. When seen again, 2 weeks later, he complained that he had not experienced any relief, that he had suffered several sleepless nights, and that he had bled profusely from his nose during the previous night. The blood pressure was 210/113 at this visit. Hexamethonium was prescribed, 500 mg. 4 times daily. About 36 hours later, at 8 a.m., one of us (P.K.) was urgently called to his home. He had pain in the lower abdomen and was unable to empty his bladder. Catheterization resulted in prompt withdrawal of over 390 cc. (25 ounces) of urine and afforded complete relief. Hexamethonium was thereupon discontinued, and no further urinary difficulties were experienced.

Hydralazine (Apresoline). This drug is a synthetic compound producing a marked decrease in peripheral vascular resistance, particularly in the splanchnic area, including the kidneys. Large doses have a sympatholytic and adrenolytic action. The drug is believed to have a preponderantly central action.[6] Bladder disturbances have been reported after the use of this product; the mechanism is not clear. Goldstein, Schloss and Cohn[7] stated that before their case there were no published reports citing urinary retention as a side effect of hydralazine. Cystometry performed by them during hydralazine therapy showed a severely hypotonic bladder with poor maximum voluntary voiding pressure. Clinically, there was a frequent desire to void, with difficulty in starting the stream. Van Duzen[8] states that hydralazine has caused complete retention.

Anticholinergic Drugs

There are many drugs with anticholinergic properties capable of blocking the transmission of nerve impulses at all ganglions. Some of these preparations are more effective at the parasympathetic ganglions and effector sites than at the sympathetic. These compounds are useful in gastrointestinal disorders to reduce motility and secretion of the stomach and intestinal tract. Pelladonna and its alkaloids are prime examples of anticholinergic drugs used for this purpose. More recently a whole new series of anticholinergic drugs have been synthesized—all quaternary ammonium compounds with varying degrees of effectiveness in blocking parasympathetic ganglions and effector plates. The manufacturers' designations of some of these preparations are: Antrenyl, Banthine and Pro-Banthine, Elorine Sulfate, Pavrine and Prantal. Synthetic drugs with anticholinergic action and resembling atropine chemically include Homatropine, Novatropine, Syntropan and, more recently, Bentyl, Centrine, Trasentine and Pavatrine. Unfortunately, both these classes of anticholinergics, quaternary ammonium compounds and atropine-like synthetic substances produce side effects in the bladder and on micturition,[9,10] the result of blockage of parasympathetic impulses. The following cases are in this group:

C.S., a 42-year-old woman, had a long history of duodenal ulcer. She was seen at home with sudden complete urinary

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retention that occurred 1 day after the beginning of Banthine therapy, 100 mg. 3 times daily. The bladder contained 1400 cc. of clear urine. The drug was eliminated, and she became free of urinary complaints. Urologic study was negative. Several weeks later a 2d trial of Banthine in smaller doses again produced retention of urine.

J.B., a 58-year-old man, was hospitalized in the latter part of July, 1954, for an attack of acute coronary occlusion with myocardial infarction confirmed by serial electrocardiograms. His hospital course was uneventful, and he was discharged improved after 1 month's stay. He had complained of epigastric distress and heartburn for several years before the cardiac episode. On his return home the complaints recurred with some severity, and he was given Donnatal, 1 tablet 4 times daily (this tablet contains a mixture of the belladonna alkaloids, hyoscyamine, 0.1037 mg., atropine, 0.0194 mg., and hyoscine, 0.0065 mg., with phenobarbital, 16.2 mg.). Within 48 hours of the first dose he had difficulty starting the urinary stream and experienced a constant desire to urinate, along with an inability to empty his bladder completely. The Donnatal was stopped, and within 24 hours the urinary difficulties were completely relieved.

Antihistamines

Urinary disturbances and retention are fairly common after the administration of antihistaminic preparations.[11-15] These effects may be due to their atropinelike activity, to potentiation of response to epinephrine or to stimulation of adrenergic nerves.[16,17] Two typical cases follow:

W.L., a 52-year-old man with Parkinson's disease was hospitalized in July, 1951, because of difficulty in urination. He noticed that the stream started adequately but, in the middle of urination, became smaller, and the volume less. With added abdominal-muscle contraction he could finish micturition with good volume and stream. He was receiving hyoscine, 2.0 mg. (1/30 gr.) 3 times daily, pilocarpine, 8.0 mg. (⅛ gr.) 4 times daily, Artane, 2.5 mg. (1/25 gr.) 3 times daily, Benzedrine, 12.5 mg. (1/5 gr.) daily, and Thephorin, 15 mg. (¼ gr.) 4 times daily. Cystometric examination revealed normal sensation, normal rise in pressure, a capacity of 400 cc., and no voiding reflex. Cystoscopy showed slight enlargement of the prostate. Thephorin was the only drug discontinued, and the urinary difficulty cleared up promptly.

M.T., a 66-year-old man who was known to have diabetes and hypertension, was hospitalized for an attack of coronary thrombosis complicated by pulmonary infarction in December, 1954. He was given 300,000 units of procaine penicillin intramuscularly every 12 hours for 3 doses. This was discontinued when a history of penicillin sensitivity was elicited from the patient. One week after the initial dose he broke out in a generalized urticarial eruption. Tripelennamine was prescribed in a dosage of 100 mg. (1½ gr.) every 4 hours. Within 30 hours, he complained of difficulty in starting the urinary stream, slight burning on urination and a frequent desire to void. Tripelennamine was discontinued, and the urinary symptoms subsided within twelve hours.

Chlorpromazine (Thorazine) is an antihistaminelike synthetic with diverse pharmacologic actions and is used clinically in a variety of conditions, including nausea and vomiting, emotional disturbances, intractable hiccups and the management of the patient with cancer who is in severe pain. The following case is typical:

B.M., a 48-year-old patient with rheumatic heart disease in chronic congestive heart failure, required full digitalization and meralluride sodium injections for relief of dyspnea and edema. Diuresis after the mercurial diuretic was uncomplicated. Because the patient began to suffer nausea, vomiting and extreme discomfort, chlorpromazine was administered, 25 mg. (⅜ gr.) 3 times daily. On the following day complete urinary retention occurred, requiring catheterization. The sequential relation between chlorpromazine and urinary retention was not recognized at the time, and the drug was unwittingly continued for several days. While the patient was receiving chlorpromazine, catheterization was required from time to time.*

Amphetamine Preparations

These are sympathomimetic agents now commonly employed in the treatment of obesity and emotional disturbances, postencephalitic Parkinsonism and barbiturate poisoning. Because of the generalized utilization of the amphetamine preparations for the control of obesity, the practicing physician frequently encounters certain urinary side effects,[16,18,19] which may be due to contraction of the internal sphincter, an inhibitory action on the expulsive musculature of the bladder, or both.[20] Loman and his co-workers[21] administered amphetamine sulfate intravenously and by means of urographic studies demonstrated markedly enlarged bladders having the appearance of a cord bladder.

Isonicotinic Acid Hydrazide Compounds

These are synthetic preparations related chemically to nicotinic acid and introduced for the chemotherapy of tuberculosis in 1951. Urinary difficulties have been described in 11 per cent of the cases of Coates et al.,[22] consisting of inability to start the stream, or delay in initiation of micturition, and frequency. Delayed starting of the stream has also been reported as a side effect by Fisher and his co-workers[23] and by Selikoff, Robitzek and Ornstein.[24] The last group believes that these effects might be of autonomic origin and the result of either the parasympathetic blocking or the sympathetic stimulating properties of the drug.

Drugs Causing Mechanical Disturbances of Urination

Mercurial Diuretics

Mercurial diuretics are employed in the treatment of congestive heart failure, edema found in the nephrotic stage of chronic nephritis and recurrent ascites and pleural effusions of diverse etiology, when the primary goal is the increased excretion of fluid via the kidneys. Spectacular diuresis is often obtained by the employment of such mercurial compounds as Mercuhydrin, Theomerin, Mercuzanthine and Salyrgan-Theophyllin. Urinary retention after the use of such mercurial diuretics is frequent.[25,26] The following cases are of this type:

A.F., a 28-year-old well developed woman with pemphigus, was on cortisone maintenance therapy after the dermatologic manifestations of the disease had been suppressed with ACTH. The minimum dosage of cortisone required for control was 50 mg. (¾ gr.) daily. On this regimen generalized edema developed. When seen in this condition she was given 2 cc. of meralluride sodium intramuscularly. Late that night her physician was called to her home because

*This case is reported through the courtesy of Dr. S. T. Friedman.

she experienced severe pain in the lower abdomen and an inability to void. Abdominal examination revealed an exquisitely tender, distended bladder, at the level of the umbilicus. She was catheterized, with immediate relief, and was then hospitalized for further study. Cystoscopic examination revealed hypertrophy of the tissue about the bladder neck. Transurethral resection was performed.

B.S., a 65-year-old man with hypertension, was admitted to the hospital for a massive upper gastrointestinal hemorrhage. This was controlled with transfusion therapy, but his hospital course was complicated by an attack of myocardial infarction associated with congestive heart failure. He responded to full digitalization and a low-salt regimen, and was discharged improved after 5 weeks. When next seen, several weeks later, he was again in congestive heart failure, with prominent ankle edema. He was given 2 cc. of meralluride intramuscularly at once. On the return visit, the next day, examination revealed that the bladder was distended and was palpable above the umbilicus. This distention was relatively painless. Catheterization was performed, and more than 90 cc. (30 ounces) of a clear urine was obtained.

Sulfonamides:

Prolonged sulfonamide therapy, under certain circumstances, can result in acute urinary retention from blockage of the urethra by sulfa crystals deposited in the urethra.[27,28]

Discussion

Mechanical and nervous mechanisms are the primary factors involved in the disturbances in urination produced by drugs. The deposition of sulfa crystals in the urethra, with subsequent blockage and urinary retention, is a clear example of the mechanical type of disturbance. In addition this group includes the mercurial diuretics. The distention effects in the urinary bladder demonstrated by Lawson, Schneeberg and Tomlinson[29] parallel, in our opinion, those observed with cardiac muscle.[30] It appears, then, that the sudden and rapid filling of the bladder that follows the use of the potent mercurial diuretics may stretch the muscle fibers beyond their physiologic capacity, with a resultant diminution in their contractile power. Urinary retention may therefore ensue. This is especially true in persons (male or female)[31,32] with a degree of vesical-neck obstruction.

The nervous mechanisms that produce micturitional difficulties may be the result of either parasympathetic blockage or sympathetic stimulation. The efferent nerves to the bladder are both sympathetic and parasympathetic.[20,33,34] The parasympathetics, the more important, supply motor fibers to the detrusor muscle, govern the tonus and the contractile mechanism and possibly supply inhibitory fibers to the internal sphincter. The sympathetics, it is generally agreed, carry motor fibers to the trigone and the bladder neck, but their effect on the detrusor muscle is a subject of controversy; some authors consider them to have an inhibitory action.[33-35]

Conclusions

Some of the newer drugs may cause disturbance in urination, such as frequency, inability to start the stream and retention. These disturbances may be mechanical or nervous in origin. Mechanical blockage may be seen in sulfonamide therapy and with the use of mercurial diuretics. Drugs such as the ganglionic-blocking agents and hydralazine, used in the therapy of essential hypertension, the anticholinergic agents, used in gastrointestinal disorders, the antihistamines, including chlorpromazine, the antituberculosis drug isonicotinic acid hydrazide, and the amphetamine preparations all appear to elicit undesirable side effects on urination by virtue of their effects on the parasympathetic-sympathetic system. An increased awareness of these side effects will lead to their prompt recognition. Discontinuance of the offending drug is usually curative.

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SPECIAL ARTICLE

PSYCHIATRY IN MODERN LIFE

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BOSTON

EVERY physician, at some time or other, is asked the question, what is modern psychiatry? And whether he is a general practitioner or some kind of a specialist, he is taxed to define and tell about this new field toward which an increasing amount of public interest is turning. In the abstract, psychiatry can be defined as a special branch of medical science, as the study and treatment of mental disease, as the investigation and classification of disorders of personality, or as a description of disturbances in the distribution of human energy, or interpersonal relations or problems of maladjustment. But psychiatry changes constantly as the borders of the medical sciences change, and each era of psychiatry is altered somewhat by the social, economic and cultural attributes of the period in which it exists. Thus, modern psychiatry is psychiatry as it is taught and practiced today and is, of course, the basis of the psychiatry of tomorrow.

But the scope of any definition is necessarily limited, and this discussion does not aim at any complete survey, however brief, of the facts of modern psychiatry; that would be a fit task for a handbook. Still less does it aim at setting down in an elementary form the rudiments of the subject; that would be a primer. Rather, these notes may be, in the Greek sense, a *historia*—an essay or an inquiry into the nature of modern psychiatry, an attempt to see whence it came and whither it tends, how it resembles and how it differs from other ways of thinking. Especially, its object is to ask and, if it may be, answer the question, What in modern psychiatry is characteristically modern?

Every school of psychiatry contains two elements. There is first what a man *thinks* about the subject, his ideologies or, if one prefers so to call them, his theories; the second is what he *does* in relation to it —his practice. In primitive ways of thinking, though these two elements are clearly to be distinguished, they are never, or very rarely, separable. In all modern schools of psychiatric thought these two elements are informed and transfused by a third impulse — that arising from each man's personal emotion toward mental phenomena, if one so wishes to call it, and his sense of dependence on or independence of his emotions: his fears, his hopes, his loves.

HISTORICAL BACKGROUND

The study of modern psychiatry is still young and struggling. To many ears the very word "psychiatry" rings with a certain dissonance. But the study of one part of psychiatry is old and honored. Some knowledge of psychiatry is necessary for the study of literature in general. The scholar, even after the most rigorous application of grammatical rules, is still occasionally driven to take into account his "psychologic" interpretations. The teaching of Shakespeare, for example, as an academic exercise, frequently bogs down at just that point. Many the hours and much the midnight oil burned in efforts on the part of tender minds to "explain" the personality of Hamlet and to tell about the reasons Shakespeare had, as a dramatist, for "creating" Lady Macbeth. Psychiatry was at one time (and in some quarters still is) regarded not as a subject worthy in itself of study — not as a part of the history of the human mind, for example — but as "ancillary," as of some service to literature or medicine as the case may be. Nothing so effectively starves a subject as to make it occupy this "ancillary" position.

Until the last decade, it was usual to speak somewhat defensively (and sometimes in an intentionally controversial manner) of leaders in psychologic and psychiatric thinking. There was little psychiatry in America (except what was developing), and most of it came from abroad. Until a few years ago, the average psychiatrist was a man who had to some extent "studied in Europe." Consequently, he brought back something slightly foreign and faintly strange — a compound in which was mixed a secondary strangeness (coming from abroad), in addition to whatever strangeness might have been inherent in the subject itself. To many people psychiatry always is strange and always will be. Just as it was once usual to call the Greek gods by their Latin names, so this country has tended to let the psychiatrist bring along and

rename a certain kind of protective veil that comes from being born in another place and from using another language. But this practice is coming to an end. Now, psychiatrists are more familiar with their technics and with their tasks and need not spend time in slaying dead lions. Americans are getting used to psychiatry and psychiatric terms without European veneer or names. Is Jupiter the same as Zeus? Is Minerva the same as Athena? But a subtler and more dangerous error remains. Like their ancestors who invested Greek gods with Latin or Roman and Alexandrian *natures,* Americans are still inclined to invest American psychiatry with European attributes and to make of it a trivial manifestation of a late, artificial and highly speculative ideology. The Greek god of Love, Eros, came to be called Cupid; he is Mickey Mouse today, but with all their newfangled pictures and images, Americans have not wholly rid their minds of the fat, mischievous urchin with his bow and arrows — a conception that would have astonished worshippers in his own city of Thespiae, where the ancient image of Eros was "an unwrought stone." And so it is with many ideas in psychiatry today: in name and in form they have changed from the shape of an unwrought stone to a fat boy and thence to a highly mechanized dwarf, or animated cartoon. One wonders how the "Oedipus complex," for example, once embraced in the concept of maternal affection, may yet be streamlined in the future, and upon what shore, by energy or aggression, it may come to rest.

Three disabilities have to some extent atrophied and well-nigh paralyzed the study of modern psychiatry. In the first place, instead of being considered as a whole, only one part, "psychology" or "abnormal psychology," has been studied. Secondly, even psychology was not studied rationally, as a whole, but in scraps, to explain certain "allusions." Thirdly, such psychology (and psychiatry, too, it must be said) as was studied was seen distorted in certain ways through the confusion of what can best be called a Victorian or post-war haze. To read some paragraphs of Watson's *Behaviorism* today can lead one to wonder that a study reduced to such inanity could still keep its hold on the human mind.

Scientific Applications

The study of psychiatry as a whole is a tardy modern growth. So long as psychiatry was divided into one true idea and the rest false (as it was in the minds of some investigators), progress was naturally impossible. The slow pressure of science introduced first the comparative and then the historical method. The facts of earlier and more recent psychiatric observations being once collected and laid side by side, it became immediately evident that there were resemblances as well as differences, and some sort of classification was possible. Then came the historical impulse, the desire to see if in psychiatry also a law of development existed, and if the facts of psychiatry succeeded each other in any ascertainable order.

From this intrusion of the comparative and historical methods, several schools of psychiatric thought long held themselves aloof. The Jungian school has been regarded as "too mystical" (an outworn phrase when used in that connection), and Freudian psychoanalysis as forming part of an exclusive stronghold, which was supposed to stand in some strange antagonism to general psychiatry (at least by some) and to general medicine, general science and logic. Certain opposing schools (several could be named) that on the surface appeared as different perhaps as any schools of thought could be were declared, in certain quarters, to be identical. Dying of these unnatural partnerships, and of their self-imposed isolations, numerous different (but not necessarily opposing) schools of psychiatric thought at last have consented to join hands with the rest of humanity and come to life again. It is probably no accident that the "anima" of Jung is about the same as the "id" of Freud and not too different from the "will to power" or "aggression" of Adler or the *élan vital* of Bergson, for that matter, to name but a few. Psychiatry, therefore, is now a subject that can be studied as a whole, not merely as "abnormal psychology," as part of the spiritual history of the human race, not as the means of interpreting a particular action, and as contrasted, not as identical with, the general science of scientists.

The study of psychiatry owes much not only to reform in method but also to a very large recent accession of material that has again and again acted as a corrective to mistaken views. To make a single example, the discovery and the clinical use of the Rorschach ink-blot test alone has forced one to see the primitive (or unorganized, if they may be called that) parts of expressions of the mind not as sociologists or economists regarded mental phenomena but rather as Jung and Freud saw them. It is realized, for example, that erotic associations not only cling around sexual objects (where they undoubtedly belong) but may also be connected with percepts of color and motion and with (other) concepts of worship and adoration, and that they are crystallized in the formal religion to which many persons adhere. The attitude of psychiatry toward sex today is much the same as that of students of Greek religion who, after study of archaeologic material and comparisons of carvings and vase paintings, came to realize that Dionysus was not only the beautiful young wine god but also an ancient tree god, worshipped as a draped post, and that the sirens were not only lovely, baleful mermaidens but also strange bird demons with women's heads.

Excavation, which used to concern itself with works of art only, now seeks for and preserves every scrap of psychologic evidence, however humble. This

has called attention to *what people do.* One discovers and studies not only the Hermes of Praxiteles but also masses of terracottas and bronzes, showing the local types under which the god or goddess was worshipped, and reads inscriptions of local rites disregarded by Homer and the tragedians. In a word, the act of excavation has been extended in two thousand years to the point where it includes psychologic excavation, and, in a sense, that is exactly what the psychiatrist does when he sets to work with a person and a situation to rediscover and reconstruct important material that might have formed the foundation and the pattern of structures erected later (and sometimes erroneously) in the building of the character or the personality. The major discoveries of the great archaeologist-psychiatrists may be the Hermes and the Venuses, but the daily work of the psychiatrist-in-ordinary may be compared to the continuous digging up of terracotta images and masses of bronzes, which also have to be interpreted in terms of the major types already discovered and classified.

Especially important in their influence on the study of modern psychiatry have been the particular investigations and the development of particular ideas in certain particular regions and locations. There is a list of cities, possibly 10, where 90 per cent of all the psychiatry in the world has been developed. Vienna, Zurich, Nancy and Paris head the list. Also important, however, are special archaeologic, paleontologic and anthropologic social and psychologic studies that have given the primary clinical findings historical and anthropologic corroboration. Archaeologically, these special discoveries in special regions may be compared to special excavations on prehistoric sites. At one time it could be said that the poems of Homer were the great medium through which the popular mythology of Greece, for example, was fixed. Originally, in psychiatry, a few names were the major ones. But just as excavations begun on the site of Troy culminating in the famous excavations at Knossos have taught something of the mythology of that region in a time before Homer, so biologic, social and anthropologic studies have added retroactively to the language and ideas of psychiatry in such a way that the first few names are no longer the entire starting point in the history of modern psychiatry.

Conclusions

The *material* of modern psychiatry, in its two departments of theory and practice, is, in the early stages of its development, much the same as that of other ages. One finds ghosts, and spirits and nature gods, ancestor worship, familiar patterns of thought and behavior, tribal attitudes (social and cultural), body worship, or anthropomorphism, the formation of a regnant set of ideas in certain individuals or groups, individual psychologies, magical and obsessive rites, purifications, prayers and sacrifices — all the common stock and the successive phases of emotional and superstitious humanity. What is characteristic of modern psychiatry is not the material but the handling of it. Among some modern psychiatrists, it is agreed that the creative imagination and a certain surplus of some kinds of energy, though never perhaps without their influence on conduct, tend to become the impulse (or prime mover) of two quite other forms of human activity, both of which are often, though wrongly, regarded as alien to psychiatry. These two forms are *art,* both literary and plastic, and *philosophy.* By this rare process, whereby certain drives are sublimated or substituted, savage elements in human nature are eliminated, and, by this purgation from ignorance, ugliness and fear (a process that psychiatrists are now beginning to understand), the deeper tendencies in man can become not only powerless to harm but also exceedingly potent for good.

MEDICAL PROGRESS

ABDOMINAL SURGERY (Concluded)

Claude E. Welch, M.D.*

BOSTON

Liver

Child's[67] monograph on the hepatic circulation and portal hypertension is an excellent summary of all known data on these subjects, together with an analysis of the published case reports of the various venovenal shunts performed to lower portal hypertension.

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Gall Bladder and Bile Ducts

Biligrafin

The introduction of intravenous cholangiography has opened an entirely new avenue of diagnosis. Typical of many enthusiastic reports is one by Glenn et al.,[68] regarding 80 patients, with delineation of the common duct in 53. The procedure was of no value in the presence of jaundice. The authors consider it

indicated particularly in the following groups of cases: the postcholecystectomy syndrome, as a preoperative cholangiogram, when oral cholecystography is not feasible, in children, in emergencies or when tumor is suspected in the porta hepatis.

The debate over the value of operative cholangiography continues with increasing vigor. Numerous studies have appeared for or against it. Hoerr[69] observes that it is valuable for many reasons: to eliminate jaundice of hepatic origin by cholecystcholangiogram; to demonstrate the location of benign strictures, particularly of the major hepatic ducts, or to determine the cause of obstruction at the sphincter of Oddi; to determine the extent of extrinsic neoplastic disease; to demonstrate common-duct calculi; and in miscellaneous indications — for example, to distinguish choledochal cyst from subdiaphragmatic abscess. He concludes that a "normal" cholangiogram is not a contraindication to an exploration of the common duct if sound clinical reasons indicate such a procedure.

Most arguments favoring operative cholangiography are based on the number of overlooked stones that remain in the common duct when cholangiography is not used, despite choledochotomy. Although McKittrick and Wilson[70] reported only a 2 per cent incidence of retained stones, the usual level throughout the country is much higher. Thus, Hicken et al.[71] in a study of 550 cases treated in 11 hospitals in Salt Lake City in which stones were removed from the extrahepatic biliary tree, showed residual common-duct stones in 20 per cent ten days later; secondary operation was necessary in 81 per cent.

Johnston, Waugh and Good[72] reviewed records of 175 patients who had had common-duct stones and postoperative cholangiograms and who were followed for a minimum of two years. Recurrent or persistent symptoms were encountered in 26 (residual stones in 12, re-formed stones in the duct in 6, stricture or ampullary stenosis in 4, and pancreatitis in 4). Reoperation was necessary in 15 of the 26 cases. Though this represents an incidence of residual stone in 8 per cent of patients, the authors do not believe that operative cholangiography would improve results because of inherent difficulties with this method. Walters,[73] from the same clinic, routinely dilates the ampulla to a diameter of 8 mm., and does not use postoperative cholangiography because he can recall only 4 cases in which a stone of the common or hepatic duct was overlooked at exploratory laparotomy.

Chlorpromazine Jaundice

An increasing number of patients have manifested severe jaundice after the administration of chlorpromazine. This has proved a serious problem because, with it, all tests of liver function and liver biopsies are typical of obstructive jaundice. Liver biopsies show bile stasis with slight evidence of cholangitis, but the only way other lesions can be accurately ruled out is by exploratory laparotomy, which can well be accompanied by cholecystocholangiography.

Cholecystectomy

Colcock and McManus[74] have presented a careful, detailed study of 1356 patients operated on in the Lahey Clinic in a five-year period for cholecystitis and cholelithiasis. The mortality for the entire group was 1.1 per cent; that of cholecystectomy was 0.9 per cent, and that of cholecystectomy and choledochotomy 1.1 per cent. Fifty per cent of the deaths were found in the 105 patients who were jaundiced at the time of operation. All patients who have gallstones are advised to have surgery, but actually only 2.1 per cent of the entire group were asymptomatic; 10.4 per cent had common-duct stones — a sharp decrease from the last report. Of those with common-duct stones 8.5 per cent had no pain; 50 per cent of patients who were jaundiced at the time of operation had common-duct stones. The incidence of common-duct stones encountered with acute or subacute cholecystitis was three times as high as that with chronic cholecystitis.

Cholangitis

Sarkisian and McGowan[75] have investigated the relation of bacteria in the bile to biliary dynamics, cholangitis and the postcholecystectomy syndrome. In 27 patients with T-tube drainage it was found that a reduction in perfusion pain pressure of the common duct below 550 mm. of water indicated cholangitis. As the level of perfusion pain pressure increased, the number of bacteria in the bile decreased.

Primary cholangitis is particularly prevalent among the Chinese. Ninety consecutive cases were studied by Cook and his co-workers.[76] The disease, if uncontrolled, progressed to liver abscesses and secondary involvement of the gall bladder. Surgical intervention consisted of the removal of any stones, drainage of the biliary tree and cholecystectomy when there was severe damage to the gall bladder. The prognosis is good.

Dilatation of the Sphincter of Oddi

Brush et al.[77] evaluated the effect of dilatation of the sphincter of Oddi performed during choledochostomy. One hundred and ninety-eight patients had this procedure, and in 230 controls the operation was the same except that the dilatation was omitted. Residual or re-formed stones were found in 10 who did not have dilatation, and in none who had it. Hospital stay and mortality were the same in the two groups. Eighty of the patients with "dilatation" actually had dilators of only 3 or 4 mm. passed, but in the others larger sizes were used.

Postcholecystectomy Symptoms

Morton[78] has operated on 20 patients with postcholecystectomy symptoms. The symptoms, including jaundice in several, were ascribed to the presence of a retained cystic-duct stump alone; the remnant varied from 1.5 to 7 cm. in length. A prolonged follow-up study after removal of the remnant showed that 18 patients were completely free of symptoms, and the other 2 had only minor complaints.

Amputation neuromas may account for residual symptoms. Hume and Buston[79] have reported 9 new cases, with 8 patients asymptomatic after removal during a follow-up period up to seven years. Bartlett and McDermott[80] recorded 2 cases in which obstructive jaundice from the neuroma developed many years after the original biliary-tract surgery.

Intrahepatic Cholangiojejunostomy

The status of this operation, first devised by Longmire, has been reassessed by Lippman and Longmire,[81] who report 5 new cases. A total of 23 now have been recorded. Follow-up study of all patients showed generally good results. The authors believe that operative cholangiography should be employed through the sectioned left lobe to determine that the largest available left hepatic duct is being used, and to assure the presence of a communication between right and left hepatic ducts.

Pancreas

Lymphatics

Evans and Ochsner[82] made a detailed examination of pancreatitic lymphatics in 30 human cadavers after India-ink injection. An extremely wide dissemination was observed. The anatomic diagrams presented make the authors doubt the value of the limited pancreaticoduodenal resection that is now carried out for cancer.

Pancreatic-Duct Pressure

Fundamental studies of common-duct and pancreatic-duct pressures were made in trained, nonanesthetized dogs by Parry, Hallenbeck and Grindley.[83] Pressure in the fasting pancreatic duct averaged 91 mm. of water, and that in the common duct 47.9 mm. This great difference tended to persist even after eating, when both pressures increased; occasionally for a brief period, as the gall bladder emptied, pressure in the common bile duct became greater than that in the pancreatic duct.

Pancreatic Tumors and Peptic Ulcerations

A significant relation has been established by Zollinger and Ellison[84] between certain tumors of the pancreas and unusual types of peptic ulcerations. They observed 2 cases of primary nonspecific ulcer of the jejunum associated with marked gastric hypersecretion and hyperacidity. Islet-cell tumors of the pancreas were discovered in both. Other cases, reported in the discussion of this paper, indicate that pancreatic tumors (either alpha or beta cell) should be suspected in any case of bizarre peptic ulceration that is refractory to the usual types of therapy.

Pancreatitis

A sound presentation of the whole problem of pancreatitis has been made by Zollinger, Keith and Ellison.[85] In a summary of acute pancreatitis they point out that the whole blood deficit averages 1500 cc. per patient, and that restoration of blood volume accounts for the value of serum albumin. Recurrent, or chronic, pancreatitis, diagnosed by a history of three or more attacks, by x-ray demonstration of calcification or by direct biopsy of the pancreas, must be treated by individualized procedures. One hundred and thirty-four cases were seen in a seven-year period, with a 12.6 per cent mortality.

In the University of Pennsylvania Hospital, Kirby et al.[86] observed 110 patients from 1946 to 1953 with acute pancreatitis. The mortality was 13.8 per cent, hemorrhage accounting for over half the deaths. The authors believe that wide drainage, when a large, tender mass and fever develop secondarily in patients with acute hemorrhagic pancreatitis, may prevent death from this complication.

Acute pancreatitis has followed transcholedochal sphincterotomy often enough that a warning note should be sounded about its indiscriminate use. Blatherwick and Pattison[87] reported 3 deaths that occurred in this fashion.

The fate of patients surviving one or more attacks of acute pancreatitis was studied by Raker and Bartlett[88] at the Massachusetts General Hospital. Of 134 patients observed, 12 per cent died of the acute attack. Thirty-two patients served as controls; 10 had recurrent attacks of pain. Fifty-one had cholecystectomy and choledochostomy; 47 had good, 2 fair, and 2 poor results. In this group 35 patients had five or more attacks. The patients with the poor results had had an unsatisfactory dilatation of the ampulla of Vater, which in this hospital is believed to be an important part of the original operative procedure. This careful follow-up study emphasizes the fact that adequate biliary-tract surgery can relieve a large percentage of patients with pancreatitis.

Warren,[89] in a discussion of chronic relapsing pancreatitis, states that a variety of surgical procedures are necessary and that no one measure short of total pancreatectomy is specific. Obstruction of the pancreatic ducts is the underlying cause and must be relieved whenever possible. Eighty-seven patients have been operated on at the Lahey Clinic, with no death in 58 cases in which a direct attack was made on the pancreas. Preference is now given to the following procedures: transduodenal exploration and dilatation of the ducts of Wirsung and Santorini;

pancreatoduodenal resection, distal pancreatectomy (when the disease is confined to that portion of the gland); and pancreatogastrostomy or pancreatojejunostomy.

Further papers have analyzed results after certain specific operations for relapsing pancreatitis. The value of prolonged external biliary drainage is shown by Priestley, Taylor and Rogers[90] in a series of cases from the Mayo Clinic. External biliary drainage provided complete relief in 62 per cent of patients who had disease in the biliary tree, and in 13 per cent in whom there was no biliary disease. An internal biliary drainage provided complete relief in 50 per cent when biliary-tract disease was present, and in 31 per cent when it was not.

Ligature of the pancreatic ducts has been suggested to produce secondary atrophy of the gland. Cannon[91] has described his experience with 6 of these operations. He believes that both ducts should be ligated. The results were not particularly promising since only 1 patient was definitely relieved.

Choledochojejunostomy after division of the common duct has again been recommended by Bowers,[92] whose patients originally treated in that fashion still show good results. Poth[93] has preferred side-to-end choledochojejunostomy, using a Y loop, to avoid the danger of common-duct stricture. He reports good short-term results. Rousselot et al.,[94] on the other hand, have treated 5 cases of relapsing pancreatitis by choledochojejunostomy, with a good result in only 1.

Caudal pancreatojejunostomy has interested many surgeons. DuVal[95] amputates the tail of the pancreas and makes pressure studies of the pancreatic duct and an immediate pancreatogram by retrograde injection of the duct. If the duct is obstructed at the ampulla of Vater, the distal end of the duct is anastomosed to a Roux-Y loop of jejunum. By this measure he has had good results in 2 cases. On the other hand, in the experimental dog, Sensenig and Bowers[96] found that such an anastomosis shortly closed over, and the ligated main duct recanalized.

Mallet-Guy,[97] who has had an extensive experience with pancreatitis, finds that left-sided pancreatectomy is often possible; he has had 14 cases with 10 good results. In other cases he prefers a very limited left-sided splanchnicectomy; this has been done in 42 cases, with 1 death and 1 failure.

All these operations are listed so that the divergent methods that are now under clinical investigation may be appreciated. It is clear that there is no panacea for the disease. All methods have failed frequently, and the decision about the proper operation may be extraordinarily difficult.

Miscellaneous Considerations

War Wounds

Sufficient data have now been collected to make a fairly accurate comparison of abdominal wounds in the Korean conflict and in World War II. Artz, Brownell and Sako[98] note that in the final eighteen months of hostilities in Korea there were 384 patients with abdominal injuries and a mortality of 8.85 per cent. This is a significant reduction from 20.5 per cent reported by the Second Auxiliary Surgical Group in World War II in patients who had the same time lag. The difference was even more significant when multiple organs were injured. With thoracoabdominal wounds, the respective mortalities were 13 per cent and 27 per cent. The reasons for the reduced mortality are helicopter evacuation, stability of the tactical situation, better anesthesia and resuscitation, and antibiotics. An average of 1.5 liters (3 pints) of blood were given before and 1.5 liters during the operation. Technically, the main difference in treatment is that with thoracoabdominal wounds, the chest injury is treated by aspiration, and thoracoabdominal incisions are avoided. The authors report 75 patients of their own, with 9 deaths. The time lag to admission was about four hours, and that from admission to surgery three hours; the operating time was two and three-tenths hours. A second report, by Aalpoel,[99] summarizes the technical procedures, and gives his individual experience with 92 cases. There were 10 deaths in his series.

Blood Transfusions

Transfusions are given so generally that every surgeon must be familiar with the complications involved. An excellent simple discussion is given by Bell.[100] The important ones are pyrogenic reactions (in 3 per cent), hemolytic reactions (in 0.15 per cent), disease transmission (viral hepatitis, syphilis and malaria), circulatory accidents, embolic accidents and reaction to grossly contaminated blood. To these must now be added citric acid intoxication, which may occur when large volumes of citrated blood are transfused. Bunker and his associates[101] have found very high serum citrate levels, particularly in the patients with multiple transfusions who have had liver disease. Since intravenous infusions of calcium salts were not effective in relieving the intoxication, avoidance of citrated blood is necessary to eliminate the danger. The effect of the citrate is to remove ionized calcium from the blood, leading to cardiac arrest.

Wound Dehiscence

Marsh et al.[102] found through-and-through retention sutures with systematic wound closure by layers to be the important technical feature in the prevention of wound dehiscence in a carefully controlled clinical study of 1000 cases. Besides the technical details, nutritional factors, mechanical factors such as violent coughing and abdominal distention and age of the patient were important.

Retroperitoneal Tumors

A comprehensive, descriptive review of 120 pri-

mary retroperitoneal tumors is presented from the Memorial Hospital, New York City, by Pack and Tabah.[103] The most common tumors were rhabdomyosarcoma, lymphosarcoma and liposarcoma. Surgical therapy was carried out in 85 cases. Four patients survived for five years without recurrence.

Ammonia Intoxication

McDermott, Adams and Riddell[104] have reviewed the normal metabolism of ammonia, defined the syndrome of ammonia intoxication and presented a series of cases in which gross disturbances in ammonia metabolism were associated with neurologic symptoms and reversible electrocardiographic changes. Intrahepatic disease or a portacaval shunt, or a combination of both, is the underlying reason why the organism cannot rid itself of ammonia. In man the intestinal tract is the most important source of ammonia, which is converted by the liver to urea, and if this is not possible, the clinical syndrome of episodic stupor is produced. This is abetted by a high-protein diet or by blood in the gastrointestinal tract. The normal serum ammonia level is 50 microgm. per 100 cc., but it may rise to 400 microgm. during these periods of intoxication.

Drapanas et al.[105] have shown that blood ammonia concentration is elevated when the symptoms of "meat intoxication" appear in dogs. In dogs, hepatic anoxia may result in an inability to convert ammonia into urea.

Thoracic Duct

Management of injuries of the thoracic duct have been notoriously difficult. Brewer[106] has investigated 24 cases of thoracic-duct fistulas above and below the diaphragm. Trauma and malignant tumors were the most important causes. In the cervical and thoracic regions simple ligation of the duct is usually successful. Below the diaphragm the treatment is generally neglected. In a case reported by Brewer, a fistula was cured by anastomosis of the thoracic duct to the hemiazygos vein.

Hydatid Disease

Although in America hydatid disease is rare, in many parts of the world it is extremely common. Jidejian[107] has described 190 patients treated by him at the American University Hospital of Beirut. One hundred and six had cysts in the liver, and 57 had cysts in the lung, whereas others were scattered elsewhere. In the liver the safest operation is a two-stage excision, the cyst being first marsupialized and later excised, after aspiration and injection of formalin or absolute alcohol. Infected cysts are treated by incision and drainage. Calcified cysts are dead and can be excised in one stage, but need to be removed only if they are causing pressure symptoms, such as jaundice.

Antibiotic Therapy

Cohn and Rives[108] have offered proof that antibiotics delivered into the lumen protect a devascularized segment of colon even at a site of anastomosis. In dogs a 5-cm. area of colon was devascularized, and an anastomosis made in the same area. All control animals died. In 8 others the same procedure was carried out, but Achromycin was injected directly into the bowel; 6 of these dogs survived.

Poth[109] has devoted much effort to the determination of the most effective method of sterilization of the intestinal tract. For patients without intestinal obstruction he now prefers a twenty-four-hour preparation, using castor oil, 8 gm. of neomycin and 12 gm. of sulfathalidine in divided doses. A more cautious preparation without the castor oil is used in subacute obstruction. In emergencies the peritoneal cavity is flooded with 200 to 300 cc. of 1 per cent neomycin solution if there has been a perforation. If there is a perforation of the bowel or resection is indicated, the lumen of the bowel is flooded with 1 per cent neomycin solution. Fifty-two patients who have required emergency closure of perforations or resections have been treated in this fashion; in no case had peritonitis persisted after operation.

Davis et al.[110] found that a single dose of 4 gm. of neomycin by mouth almost completely suppressed all intestinal bacteria without producing toxicity or overgrowth of yeast or fungi. In an illustrative case, all organisms were suppressed at the end of a twelve-hour period, and all but the staphylococcus remained suppressed for twenty-four hours more.

Unfortunately, pseudomembranous enterocolitis remains a serious complication of antibiotic therapy, particularly after colonic resection. The broad-spectrum antibiotics too often have allowed the development of a virulent staphylococcus that has rapidly led to death. Many more reports of this usually fatal disease have appeared. Typical of the group is a series of 8 cases reported from the Massachusetts General Hospital by Speare.[111] A more extensive list of papers was given in the previous Medical Progress report.

Comparable groups of patients prepared for intestinal surgery by neomycin and by a combination of neomycin and oxytetracycline were studied by Pettet and Judd.[112] Enterocolitis occurred in 6 of the 71 patients with the combination, and in none with the neomycin. The authors note in their discussion, however, that the disease has been noted after neomycin alone, and they assume that wider use of neomycin will lead to more infections.

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MEDICAL INTELLIGENCE

A NEW SOLUTION FOR THE APPLICATION OF ELECTROCARDIOGRAPHIC ELECTRODES TO THE SKIN*

EMANUEL GOLDBERGER, M.D.†

NEW YORK CITY

FOR the past two and a half years, I have been successfully using a hitherto undescribed solution, containing a synthetic detergent, which is applied to the skin when one is taking electrocardiograms.

I have experimented with numerous detergents. At present, I am using sodium lauryl sulfate (Duponal C) in approximately 5 per cent concentration. This is dissolved in a solution containing approximately 7 per cent salt.

PREPARATION

The required volume of water is boiled, and the salt added and dissolved. Then the sodium lauryl sulfate is added. Part of the sodium lauryl sulfate will precipitate because of the presence of the salt; it is not necessary to remove the precipitate.

APPLICATION

The container is shaken, and the solution is then dabbed on the skin with absorbent cotton, or rubbed very lightly until suds begin to form. The metal electrocardiographic electrodes are then applied, and a tracing is taken in the usual way.

DISCUSSION

The use of a solution containing a synthetic detergent has five advantages. In the first place, the detergent cleanses the skin. Secondly, it acts as a wetting agent and penetrates dry, thick skin. This is especially valuable on the left leg, whose resistance is usually much higher than that of the arms.‡ Thirdly, the

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‡Goldberger, E. *Unipolar Lead Electrocardiography and Vectorcardiography.* Third edition. 601 pp. Philadelphia: Lea & Febiger, 1953.

detergent acts as a good electrolyte. Fourthly, because of these properties, the solution can be applied to the skin without rubbing, or with minimal rubbing. Finally, the detergent prevents the salt from corroding the metal electrodes even if they are not washed after use (one reason for this is the high pH of the solution).

I have not encountered any skin reactions from the use of the detergent. I might also mention that ordinary soap dissolved in salt is not effective, nor is ordinary saline solution.

Summary

The preparation and advantages of a synthetic detergent, sodium lauryl sulfate, dissolved in saline solution, for use when electrocardiographic electrodes are applied to the skin, is described.

EPIDEMIOLOGY IN COUNTRY PRACTICE

John Pemberton, M.D.*

BOSTON

DR. William Pickles, a general practitioner of Yorkshire, England, was the lecturer at a meeting on July 20 at the Harvard Club, Boston, organized by the Massachusetts Academy of General Practice. Dr. Pickles is no newcomer to Boston, having delivered the Cutter Lecture at the Harvard School of Public Health in 1948. Since that occasion he has lectured in Australia and Africa and has been elected the first president of the recently formed British College of General Practice.

On this occasion he spoke of the unique opportunities of the family doctor who practices in a sparsely populated rural area to make original and important observations on the incubation and infective periods and on the modes of transmission of infectious disease. He recalled how he first started practice in the village of Aysgarth in 1910. At that time some of the remote farmhouses of the practice, which includes 8 villages and several hamlets scattered up and down "broad Wensleydale," could be reached only on horseback or on foot. When trudging across the snow-covered fields to some lonely cottage he was often reminded, he said, of the lines of Christina Rossetti:

> Does the road wind up hill all the way?
> Yes, to the very end!

Without making light of the hardships and often modest remuneration of the country doctor the speaker made it clear that he had enjoyed his life as a general practitioner of medicine among his moorland patients. "I've had a lot of luck in my life," he said, referring to the opportunities that he had had to make the observations that established his reputation. It may be remarked that such opportunities have occurred to many others and that such achievements as his need a receptivity of mind and the imagination to perceive new relations between phenomena and the patience of a beaver to extract new and precise facts from the crude drama of nature. By such efforts Budd, in rural Somerset, unraveled the mode of spread of typhoid fever, Snow was able to give the advice necessary to bring to an end an epidemic of cholera in London, and Pickles could show that catarrhal jaundice was an infectious disease transmitted from one person to another with an incubation period of about twenty-eight days. This disease, incidentally, later became one of the chief causes of invalidity in the Allied troops during World War II and delayed the opening of the battle of El Alamein for three days.

When he first went to Wensleydale communications were tenuous, and visiting between friends and relatives in these widely separated villages was uncommon and largely confined to a few important festivals each year. Frequently, the village fete, a marriage or a funeral provided Dr. Pickles with the event he sought, "the short and only possible exposure." His observations on the incubation period of infectious hepatitis were particularly important, for at that time the infectious nature of "catarrhal jaundice" was not generally appreciated. During an epidemic of the disease that started in 1928, out of a population of less than 6000 in the dale 250 contracted the disease, of whom the speaker attended 115. In one village an outbreak was traced to a girl who, although confined to bed with jaundice, insisted on getting up to go to the village fete, where she infected 5 others; they all came down with the disease between twenty-seven and thirty-four days later. It is the custom in most of the villages of the North Riding of Yorkshire for a local club or "pub"' to organize an outing twice a year. These often take the form of a coach trip at Christmas time to the pantomime at Leeds and another to the seaside resort of Scarborough in the summer. These cities came to serve, as the speaker wryly remarked, as the replenishers of the bacterial flora of the dale.

Dr. Pickles was the first to describe Bornholm disease or epidemic myalgia in Great Britain, a story that he has already related in the *Journal*.* He told how in 1933 he was called by a young farmer to see his son, a boy of two and a half years, who had been attacked suddenly by severe pain in the upper abdomen. The boy had a temperature of 101°F.; his alae nasae were working and he had a respiratory rate of 60 per minute. A diagnosis of lobar pneumonia was made. By the next morning the boy had apparently recovered. The mother was reassured and told that her son was quite well again. However, on the next

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*Pickles, W. N. Sylvest's disease (Bornholm disease). *New Eng. J. Med.* **250**:1033-1036, 1954.

day, his distressing symptoms returned, and the doctors were confounded. Recollecting later that he had received from Dr. Ejnar Sylvest, a general practitioner of Copenhagen, a description of a similar condition occurring in the island of Bornholm, Dr. Pickles realized that he was dealing with the same disease.

The methods employed by him in his lifelong study of epidemic disease have been simple. He described how he records the name of the patient and the first day of the disease in his pocket diary as he goes on his rounds and how these are later transcribed to time charts by Mrs. Pickles, who uses the appropriate symbol for each disease and records them alongside the name of the village where the case occurred. These clear and elegant charts, some of which are published in his book *Epidemiology in Country Practice*, reveal at a glance the epidemic situation in the different villages over a period of three months at a time. Records of dysentery, influenza and tonsillitis have been kept, as well as the more specific types of infectious disease.

It is now widely recognized that there are many ill defined short or minor illnesses, or slight attacks of severe illness such as poliomyelitis, that do not cause the sufferer to be admitted to a hospital and therefore brought into the orbit of "high-powered research." The British College of General Practice has formed a research section that is trying to advance the collection of accurate records of such conditions by general practitioners, who in different areas are pooling their observations to obtain sufficient numbers of cases within a fairly short period. This appears to be a promising field for discovery, and whatever success it achieves may be attributed, in part at least, to practitioners like William Pickles, of Aysgarth, who by making observations in one community over a lifetime have proved that some of the secrets of disease may be discovered by the fascinating if arduous methods of shoe-leather and pocket-book epidemiology.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41511

PRESENTATION OF CASE

A twenty-eight-year-old single woman was admitted to the hospital because of seizures and mental deterioration.

Four and one-half months before admission the patient had her first seizure. The onset of the seizure was not observed, but when she was found by her mother she was lying on one side with her arms flexed, legs extended and tongue bleeding; her respirations were deep and rapid, her eyes were closed and saliva was running from her mouth. There was no fecal or urinary incontinence. After this she slept for two and a half hours and upon awakening had complete amnesia for the event. One hour later she had a second seizure that started with "ah, ah, ah," vocalization and was followed by stiffening of the entire body with clenching of the jaw, flexion of the arms and extension of the legs. Immediately afterwards there were clonic movements of all four extremities. The seizure lasted about five minutes and was again followed by sleep and total amnesia. She then had three more similar seizures in close succession that same day and was immediately hospitalized in another hospital and started on Dilantin. The seizures ceased and she remained in the hospital three days during which a neurologic examination and lumbar puncture were reported as negative. However, an electroencephalogram was reported as showing severe cerebral dysrhythmia, more marked over the left hemisphere. She was discharged on Dilantin, 90 mg. four times a day. She remained at home for a few weeks during which it was noted that she was tired much of the time, sleeping ten to twelve hours daily, and had some slight difficulty in finding and forming words. However, she was able to carry on successfully as a student of occupational therapy in another city for two months. When she returned home her parents again noted that she had difficulty in finding words and slight difficulty in walking. Also she complained that she could not write with her right hand and could not "think straight" as if her "mind would not react." The Dilantin dosage was reduced to 90 mg. three times a day, but shortly after this she had another seizure similar to the previous ones. She was again put on Dilantin, 90 mg. four times a day. Then the patient began to complain of generalized headaches and had several episodes of nausea and vomiting. Another neurological examination performed one month before admission was reported as negative. A lumbar puncture at this time yielded a fluid under an initial pressure equivalent to 160 mm. of water, with a total protein of 11 mg. per 100 cc. The electroencephalogram still showed a diffuse abnormality especially on the left side. The anti-

convulsant therapy was changed to mysoline, 1 capsule four times a day. After discharge she began to complain of tinnitus in both ears, morning headaches with nausea and occasional vomiting, weakness and anorexia. Her difficulty in finding words increased and during the last few weeks before admission she was unable even to take care of herself. She became unable to walk without assistance, could not use the right hand, and periodically drooled from the right side of the mouth. The disability with the right hand

FIGURE 1. *Left Internal Carotid Arteriogram, Anteroposterior View.*
The anterior cerebral artery is displaced across the midline to the right.

was variable; she was able to use it better at some times than others. She lost 15 pounds in one and a half months.

The patient was born at term of an uneventful pregnancy and normal labor. During the neonatal period a port-wine mark involving the right cheek, eye and forehead and left temple were noted. The right pupil was observed to be larger than the left one and the sclera of the right eye was described as "red-colored." Her development was normal in all other respects. She began to speak and to walk without assistance at twelve months and was toilet-trained at fifteen months. The port-wine stains did not increase in relative size. She was never able to distinguish more than darkness and light with the right eye. She did well in school and completed college. She was able to teach school for several years. Four years before admission she submitted to a series of plastic operations and tattoos during which the right eye was enucleated and replaced by a prosthesis. The family was told that the eye contained "a lot of bone." Afterwards she took a course in occupational therapy and was in the process of obtaining practical training when the present illness began. She had no history of head trauma, meningitis, encephalitis or jaundice. There was no family history of birth marks, diabetes or epilepsy. One brother was normal and well at the age of twenty-three years.

Physical examination revealed a tall, thin woman with a disfiguring hemangioma in the distribution of the first and second divisions of the right trigeminal nerve and a smaller one in the left temple. Her reactions were slow but her responses, though meager, were pertinent. Occasionally she could not express herself; pausing and groping for a word or phrase, and not finding either, she would either terminate her thought or substitute another word or phrase. Surprisingly enough she usually named common objects accurately. Spoken commands were followed but there was a tendency to confuse the right and left hand and she perseverated in speech and action. She read slowly and could write a phrase of 3 to 4 words with the left hand. She could not write with the right hand. The sense of smell was intact. The visual fields were full. There was a well fitted prosthesis in the right orbit. The left optic disc was normal. The extraocular muscles were normal and there was no nystagmus. The left pupil was 3 mm. in diameter and reacted to light and on accommodation. There was a right hemiparesis involving the face, arm and leg. The

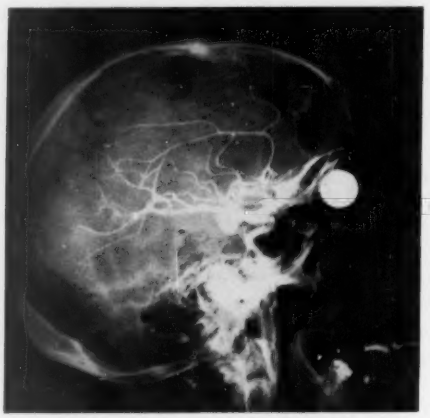

FIGURE 2. *Left Internal Carotid Arteriogram.*
The middle cerebral artery is displaced inferiorly.

tendon reflexes in the right arm were ++ and in the left +. The abdominal reflexes were absent bilaterally, and the knee jerks and ankle jerks absent even with reinforcement. The plantar response was equivocal on the right and flexor on the left. The right leg was relatively stronger than the right arm. There was a slight inconstant defect in position sense and in tactile localization in the right arm and leg, but pain, touch, vibration and number writing were the same bilaterally. A grasp reflex could be elicited in each hand when her attention was distracted. She was able to use the right leg quite well in walking with only slight scuffing of toes. Her balance was fairly normal and tests of co-ordination were performed well but more slowly and as though after greater deliberation on the right side.

The temperature was 98.8°F., the pulse 70 and the respirations 14. The blood pressure was 112 systolic, 70 diastolic.

Urinalysis was negative. Examination of the blood

revealed a hemoglobin of 13.0 gm., and a white-cell count of 3000, with 53 per cent neutrophils, 38 per cent lymphocytes, and 9 per cent monocytes. The fasting blood sugar was 89 mg., the nonprotein nitrogen 22 mg. and the serum cholesterol 274 mg. per 100 cc. The sedimentation rate was 12 mm. in sixty minutes. The platelet count was 135,000 and the prothrombin time 55 per cent of normal. The stool was guaiac negative. An electroencephalogram showed voltages increased with 3 per second delta waves bilaterally, more on the left. No abnormal rhythms were seen. There was no increase in abnormality with over-breathing or "photic driving" with a stroboscope. The roentgenograms of the chest were normal. Plain films of the skull showed a small area of increased density on the inner table in the left temporal region. The posterior clinoid processes were thin and poorly calcified.

The patient had several severe morning headaches with vomiting and some worsening in her ability to read but otherwise the clinical status remained essentially unchanged. A lumbar puncture on the second day showed fluid under an initial pressure equivalent to 240 mm. of water. The cerebrospinal fluid was clear and colorless, contained no cells and a total protein of 37 mg. per 100 cc. A positroencephalogram and asymmetrogammagram on the fourth hospital day showed a definite concentration in the posterior frontal area on the left side. A left carotid arteriogram on the seventh day showed marked shift to the right of the left anterior cerebral artery and downward displacement of the left middle cerebral group (Fig. 1 and 2). On the ninth hospital day she had two episodes of a sensation of extreme heat all over the body; she became flushed and perspired profusely. These lasted about five minutes and were separated by an interval of an hour. Also she had severe headaches through most of the day with numerous episodes of retching. Breathing ceased at eight o'clock on the morning of the tenth hospital day.

Differential Diagnosis

Dr. Paul I. Yakovlev*: In the presence of facial angioma, naturally, the first thought would be to consider Sturge–Weber disease, with angiomatosis of the meninges and the brain. There are, however, certain features in the illness of only four months' duration that would be unusual in Sturge–Weber disease. One unusual feature is that this twenty-eight-year-old woman with facial angioma since birth apparently had shown no signs pointing to intracranial angiomatosis until she began to have seizures, rapidly deteriorated mentally and had right hemiparesis and speech disturbances. Secondly, the fact that the ventriculogram had shown a shift of the ventricular system to the right indicates, of course, that there was an expanding, space-occupying lesion. That would not be likely to be an angioma, which does not grow rapidly and rarely creates a significant ventricular shift. One must, therefore, seriously consider a neoplasm such as a so-called central neurinoma or one of the tumors of spongio- or neuroblastic type as occasionally occur in patients with neurofibromatosis, tuberous sclerosis and other neurocutaneous hyperplastic malformations. This would be a more likely possibility than intracranial angioma. There was some tendency for a gradual increase in the cerebrospinal fluid pressure and in the protein content. At the beginning of the illness the total protein was 11 mg.; some three to four months later it was 37 mg. Similarly, the intracranial pressure at the first lumbar puncture was equivalent to 160 mm. of water; on the second it was equivalent to 250 mm. of water. These are slight changes, yet significant in their trend.

This is a difficult case. I have made two suppositions. One was that there was an intracranial angioma and the other, that there was a true neoplasm such as may occur in association with ectodermal dysplasias such as this patient had. If this should prove to be the case we should not perhaps have learned much. But there are other less likely possibilities that should also be considered. There may have been some degenerative disease of the brain altogether unrelated to the facial angioma, such as some form of diffuse demyelinating disease, diffuse sclerosis or encephalomyelitis.

The x-ray films should be characteristic if it were Sturge–Weber disease. It would be interesting to see them.

Dr. C. C. Wang: The plain films of the skull show an area of bony density in the left temporal bone internally, which I think represents an osteoma. The clinoid processes are well calcified and the sella turcica is not enlarged. No other unusual calcification is seen within the skull. A left carotid arteriogram shows obvious displacement of the anterior cerebral artery to the right; the middle cerebral artery as seen in the frontal projection lies in fairly normal position (Fig. 1). There is no evidence of a subdural hematoma. There is a prosthesis of the right eye.

Dr. William H. Sweet: You may want to show the lateral arteriogram in which one sees the middle cerebral artery in the lateral view.

Dr. Wang: The middle cerebral artery is displaced inferiorly (Fig. 2).

Dr. Yakovlev: Pushed down.

Dr. Wang: Yes.

Dr. Yakovlev: The findings in the x-ray films are then consistent with an intracerebral mass in the left frontoparietal region?

Dr. Wang: I would place the lesion in the left parietal region.

Dr. Yakovlev: More posteriorly than the frontal? That could be consistent with the clinical history of apraxia and aphasia. It seems, however, that the apraxic and especially the aphasic disturbances were in the form of paroxysms of inability to find words;

*Assistant clinical professor of neurology and curator, Warren Anatomical Museum, Harvard Medical School.

all signs, at any rate, point to the left posterior frontal or anterior parietal region.

DR. ROBERT S. SCHWAB: The electroencephalogram is abnormal on both sides and evident on all the runs; it is more abnormal on the left than the right. There are slow waves in the left frontal and in the left parieto-occipital regions. The rather flat line between the central and parietal region on the left may be over a mass that is not electrically active. It is not seen on the other side in the same region. There are no seizure patterns possibly because she was taking 4 tablets of mysoline a day. I do not think we did an electroencephalogram when she was not taking this drug.

DR. YAKOVLEV: The abnormality in the electroencephalogram appears then to be referable more to the area of the central fissure?

DR. SCHWAB: Yes; over the central parietal region. I think the slow activity is more consistent with an expanding lesion than a scar. There are no spikes; the picture is the kind seen in a subdural hematoma, abscess or tumor. The fact that the abnormality is on both sides might give some hint that it is deep and large. There is an abnormal record. There is no normal rhythm on either side, but the abnormality is definitely localized to the left central parietal region.

DR. YAKOVLEV: The roentgenographic findings in the skull certainly do not support the notion that she had an intracranial angioma, but rather that she had a neoplasm of glial type. The angioma usually shows such a characteristic pattern of calcification that it is unmistakable. There is no such evidence in these films.

DR. BENJAMIN CASTLEMAN: Before you saw the roentgenograms you were thinking of angioma, but now you think it is a glioma. Is that correct?

DR. YAKOVLEV: Yes; a glioma of some sort?

DR. CASTLEMAN: Dr. White, what do you think she had?

DR. JAMES C. WHITE: I should wonder whether this port-wine stain was an indication of an arteriovenous malformation or hemangioblastoma, which might have bled, but since there was only a four and a half month history and this x-ray film shows no abnormal blood vessels, I should exclude that. In the arteriograms the striking finding is the manner in which the vessels are pressed downward. I do not see any abnormality in the anterior cerebral arteries. I do not see any abnormal vessels. I am coming around to Dr. Yakovlev's idea that this was a glioma. The positroencephalogram, when there is an astrocytoma, does not pick up as much positron emitting arsenic, as it does when there is a meningioma or a more malignant tumor. Moreover, with an astrocytoma one might expect seizures for longer than four months and the progress would not have been so rapidly downhill. Therefore I think that she had a malignant glioma. With a glioblastoma multiforme, which is the most common glioma, one often sees abnormal vessels, which I do not see here, but I suppose that is the most likely diagnosis. I should like to ask Dr. Sweet why he withheld surgery if he thought it was a tumor.

DR. SWEET: The patient's craniotomy was planned for the morning of the day she was found dead in bed. The terminal course in the last fifteen hours was interesting. When I talked with her and her parents late in the afternoon of the day before operation she was alert, briskly responded to questions, and complained of no headache. In patients in whom we fear an impending disaster from an intracranial space-taking mass, which usually takes place in the form either of medial herniation of the temporal lobe against the upper brain stem or of a downward herniation of a portion of the cerebellum to the foramen magnum, we usually find a premonitory drowsiness, increasingly severe headache, pupillary inequality or nuchal rigidity. These signs were not present in this patient; in particular the lack of neurologic change over the past several days had led me to have no suspicion that she was in this precarious condition. We delayed the operation waiting for improvement of the blood picture. The white-cell count was down to 3000 and the platelets were only 135,000. Dr. Jacobson saw her; perhaps he would like to comment on his appraisal of the blood picture.

The history of probable diencephalic autonomic seizures is worth mentioning. The account was obtained from a relative after the patient had died. These were spectacular episodes. While she was talking with her family the evening before she died, she suddenly broke out into a profuse perspiration. They noted that she was grossly flushed on the face and exposed portions of the chest. She became very apprehensive, threw off the bed clothes, and took off her pajamas. Because she was perspiring so profusely the window was opened. This all subsided within five minutes and she was chatting as she had been before, but now complained of severe headache. About an hour later she had another of these episodes; it subsided just as abruptly and she went to sleep. She never recovered consciousness, being found dead in bed about eight o'clock in the morning. In retrospect I think that it is important for us to leave orders that in the event any unusual manifestations do occur in patients with increased intracranial pressure the resident or attending physician be called at once. I think we would have suspected that this patient was having a temporal lobe herniation from the diencephalic autonomic seizures, since the localizing evidence of the main lesion pointed to the frontal lobe.

DR. WHITE: You might be thinking about a report in the literature about these. Penfield back in 1929* mentions that in the diencephalon seizures the lesion must come close to the lateral walls of the third ventricle and that a deep frontal lobe lesion will do that. Have you ever run across them as a sign of temporal lobe herniation? She never had an aura of smell or bad taste.

*Penfield, W. Diencephalic autonomic epilepsy. *Arch. Neurol. & Psychiat.* **22**:358-374, 1929.

DR. SWEET: No; the seizures are adequately described in the protocol.

DR. WHITE: One other point ought to be put in for the record's sake: although there was no evidence of pulmonary neoplasm, this could perfectly well have been a metastatic lesion in the brain.

DR. WANG: The x-ray films of the chest are normal.

DR. WHITE: That does not necessarily exclude metastases to the brain.

DR. SWEET: I might also mention that the radioactive arsenic scans, which are described under the heading of positroencephalogram and asymmetrogammagram, gave so strikingly abnormal and focal a pattern that it was our impression that they sufficed to localize the site of the craniotomy. It was on that basis that we planned the bone flap before the patient was found dead.

DR. BERNARD M. JACOBSON: I saw the girl briefly the afternoon before she died and investigated the hematologic status. The initial white-cell count was said to be 3000, but when it was repeated a few days later it was 6200. I found the blood smear to be essentially normal and the platelets not decreased.

DR. SWEET: I might supplement that with the thought that the mysoline with which she was being treated has been known to produce leukopenia; the leukopenia tends to disappear once the patient has been taken off the drug.

DR. GEROLD SCHIEBLER: I was wondering whether Dr. Sweet thinks that the ACTH may have played some part in the death.

DR. SWEET: We discussed that at the time. This patient did, at Dr. Jacobson's suggestion, receive hydrocortone given intravenously in a very slow drip. I believe a total of approximately 1000 cc. containing 100 mg. of the drug ran in in a period of about fourteen hours. The injection began at 6 o'clock in the evening and was still running in slowly at 8 o'clock the next morning. I think it is impossible to be sure, but it is conceivable that that too played a real part in tipping the scales in the wrong direction. Both the fluid given and fluid retained incident to sodium and chloride retention induced by the drug might have aided in provoking the tentorial pressure cone.

CLINICAL DIAGNOSES

Brain tumor, left hemisphere.
Hemangioma of face.
Convulsive seizures, grand mal type.

DR. PAUL I. YAKOVLEV'S DIAGNOSES

Glioma of brain.
Temporal pressure cone.

ANATOMICAL DIAGNOSES

Glioma, mixed astrocytoma and glioblastoma multiforme, of left frontoparietal lobe.

Temporal and cerebellar pressure cones, left, marked.

Pulmonary edema and congestion.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy revealed that the main disease was in the brain. The remainder of the body showed some edema and congestion of the lungs. Dr. Hakim will tell you about the brain.

DR. SALOMON HAKIM: When the calvarium was opened, we focused our attention on the region of the increased density noted in the x-ray film and found a mass consistent with a benign hyperostosis. This mass grew from the inner table of the left temporal bone, was not adherent to the dura mater and did not cause any disturbance to the cortex of the brain. When the dura mater was opened, the brain immediately bulged out indicating increased intracranial pressure. The convolutions were flattened, the flattening being more marked in the left cerebral hemisphere, particularly in the frontal region. On the lateral aspect between the superior and middle frontal gyrus there was a bulging mass that was easily palpated. The sulcus between the superior and the middle frontal gyri was completely obliterated. There was atrophy of the right optic nerve as a result of the enucleation. The left temporal uncus was markedly herniated, with some compression of the brain stem in this region. On the right side also there was some temporal herniation. Both cerebellar tonsils were also herniated, but to a lesser degree in comparison with the temporal herniation. I believe that the compression of the brain stem produced by the herniation of the temporal lobe and both cerebellar tonsils would explain the death of the patient. The coronal sections through the brain showed a cavity measuring 3 cm. horizontally, 2 cm. vertically and 5 cm. in the anteroposterior direction and filled with yellowish transparent material. This cavity was located in the left frontal lobe and extended backward into the Rolandic region. One small nodule of the tumor projected into the cavity. The white matter surrounding the cavity was yellowish, and somewhat edematous, the edematous white matter extending backward near to the occipital lobe.

The microscopical preparations of the tumor near the cystic cavity showed tumor formed by glial elements of the astrocytic series. It was not possible to classify this tumor in one category because in different areas of the tumor there were different types of glial tumor cells. In one area the growth was consistent with astrocytoma, so that a biopsy taken in that area would have been diagnosed as astrocytoma (Fig. 3). In another field there was more undifferentiation consistent with astroblastoma; in still another field there was pleomorphism, endothelial proliferation and mitoses — as seen in glioblastoma multiforme (Fig. 4). The whole microscopical picture was consistent with a glioma of the astrocytic series, which had undergone malignant and cystic degeneration. I

should like to ask Dr. Kubik to comment on the microscopical sections.

DR. CHARLES S. KUBIK: We have had other cases in which areas of an apparently well differentiated

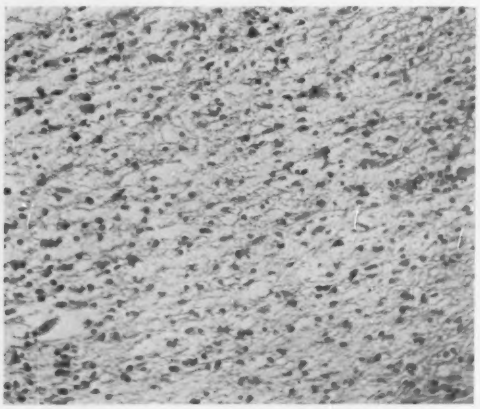

FIGURE 3.

glioma had a more malignant appearance; that is exemplified very well in this lesion in which in some parts one would not hesitate to make a diagnosis of astrocytoma while in other parts as Dr. Hakim has shown you, one would make the diagnosis of glioblastoma multiforme. In this case the symptoms were of short duration but in some the history has been quite long, and inconsistent with a diagnosis of glioblastoma multiforme from the very beginning, and there is reason to suspect that they were cases of astrocytoma that had undergone malignant change.

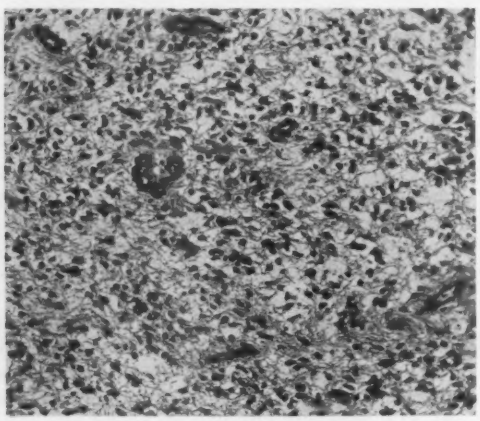

FIGURE 4.

DR. YAKOVLEV: The cortex of the second frontal gyrus overlying the cyst was not only compressed and swollen but also appeared to be abnormally wide.

DR. KUBIK: The convolutions were quite wide, as if invaded by tumor.

DR. YAKOVLEV: Was there any architectural abnormality in the cortex of the second frontal gyrus?

DR. HAKIM: No architectural abnormality could be seen, except for the extension of the tumor into the cortex from the white matter. The more malignant portions of this tumor were in the periphery away from the cystic cavity.

DR. YAKOVLEV: It began, then, deep in the white matter as astrocytoma and spread to the cortex, becoming there a malignant glioblastoma.

CASE 41512

PRESENTATION OF CASE

A fifty-four-year-old man was admitted to the hospital because of cough.

For ten to fifteen years the patient had had a chronic cough productive of white sputum. Four years before admission he had an episode of fever. He could not recall any associated cough or pain in the chest. Ten months before admission he had an episode of fever and cough that persisted for a week or so. X-ray films at another hospital revealed partial atelectasis, cavitation and a suggestion of a mass in the right upper lobe (Fig. 1). He remained in the hospital for one week during which the x-ray film of the chest showed improvement. Two weeks before admission fever, chills and a slight cough developed. He was hospitalized and x-ray films again demonstrated

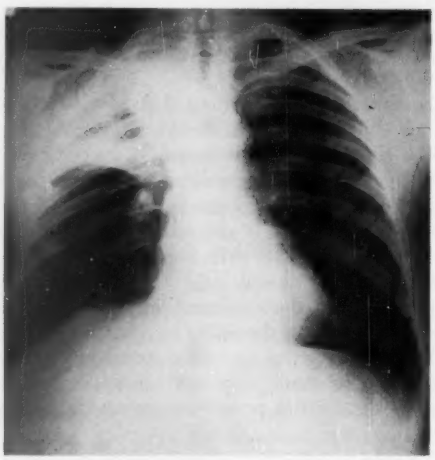

FIGURE 1. *Roentgenogram of the Chest, Showing Right Upper Lobe Atelectasis with Large Areas of Cavitation.*

atelectasis, a suggestion of a mass and several cavities in the right upper lobe. Bronchoscopy was said to show inflammation. He improved with penicillin therapy although weakness and sweating persisted.

There was no history of hemoptysis or exposure to tuberculosis. He smoked three packages of cigarettes a week.

Physical examination revealed a well nourished man. There were increased tactile fremitus at the right pulmonary apex and fine crackles anteriorly in this region. Slightly diminished movement of the

right diaphragm was noted. The remainder of the examination was negative.

The temperature was 98.4°F., the pulse 100 and the respirations 20. The blood pressure was 140 systolic, 92 diastolic.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 12.8 gm. per 100 cc. and a white-cell count of 8400, with 72 per cent neutrophils.

FIGURE 2. *Roentgenogram of the Chest, Showing Persistent Atelectasis of the Right Upper Lobe, Somewhat More Marked than in the First Examination.*
The density immediately above the minor septum, however, has cleared.

X-ray films of the chest showed narrowing of the bronchus of the right upper lobe with atelectasis of the right upper lobe (Fig. 2). The trachea was displaced very slightly to the right. No definite mass was seen. Peripherally in the right upper lobe there was cavitation and scattered fluffy areas of increased density, which were most dense in the upper portion of the lobe. Bronchoscopy revealed narrowing of the right upper lobe orifice with small patches of fibrinous exudate. Its divisions could not be identified. There was no evidence of ulceration or endobronchial tumor. The right middle and lower lobe orifices were reddened, but otherwise normal. The left bronchial tree appeared to be normal. Smears taken from the right upper lobe were negative for acid-fast bacilli. Cytological examination for tumor cells was doubtful.

On the sixth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ARTHUR S. PIER, JR.*: The point that impressed me immediately was the treatment that this man received. Ten months before entry when he was in another hospital, there were some atelectasis of the right upper lobe, evidence of bronchial disease, cavitation and question of a mass. As far as I can tell nothing much was done. Ten months later when he seemed to show much the same picture in the x-ray films except that there was no definite mass, he was operated upon in this hospital within six days. There is no indication that an assiduous search was made for tubercle bacilli: there is no record of sputum examination, gastric examination, culture of sputum or guinea pig inoculation. I suppose that a lobectomy was done, and that the opinion was that the right upper lobe was in such poor condition that it was not only relatively useless but was a hazard and would eventually have to be removed whatever disease it contained.

Passing on to the question of diagnosis, I should think that tuberculosis was the most likely answer. In fact I cannot think of anything else that is more likely here. According to the radiologists there was cavitation and scattered fluffy areas of increased density in the right upper lobe which would be fully consistent with a parenchymatous pulmonary tuberculosis, and a narrowing of the bronchus, which would go perfectly well with endobronchial tuberculosis.

How about tumor? I do not think that we have sufficient grounds to make a diagnosis of tumor. There was a suggestion of the presence of a mass in the x-ray films taken in the other hospital, but it seems to have disappeared in the x-ray film taken here. I wonder if the mass represented an area of pneumonitis beyond an obstructed bronchus, which improved with penicillin therapy. All the evidence, I think, points to an inflammatory constriction of the bronchus; there was no clear-cut evidence of neoplastic involvement. The bronchoscopy was not particularly helpful; it showed no definite distortion, fixation or rigidity to support cancer, but reddening of the orifices of the middle and lower lobe bronchi is more consistent with an inflammatory process than a neoplastic one. There is the question of the right leaf of the diaphragm not moving as well as the left on physical examination. This finding, if confirmed by fluoroscopy, might indicate tumor invasion of the right phrenic nerve, but without good fluoroscopic evidence of poor motion or fixation of the diaphragm, I should not pay too much attention to this finding.

There are other infectious lesions besides tuberculosis that he could have had, such as a fungous infection of the right upper lobe. Fungous involvement of the lung can look like tuberculosis but the patient does not appear to me sick enough for such an infection. The process was present for ten months at least and seems to have been completely unilateral, which I think would be unusual for fungous involvement.

May I see the x-ray films?

DR. RICHARD V. WILSON: We have the films taken ten months previously (Fig. 1) and films taken ten days before admission. I cannot answer the question about the diaphragmatic movement, as he was not fluoroscoped. There is the same degree of involvement in the initial films as in the later films. There is

*Assistant physician, Massachusetts General Hospital.

atelectasis of the right upper lobe, the horizontal fissure being elevated. I am uncertain about the position of the mass, which had been suspected on the basis of the outside films. On our films there is nothing that I can definitely call a tumor. There is considerable change in the periphery of the atelectatic right upper lobe with multiple scattered areas of increased density and at least one area of cavitation of good size and a number of smaller ones (Fig. 2). The right upper lobe bronchus is not adequately shown in any of the films.

DR. PIER: Is there hilar adenopathy?

DR. WILSON: There is no obvious hilar adenopathy. The right leaf of the diaphragm is elevated more than usual, but this has been of the same degree in all the examinations.

DR. PIER: There was very little change in a year's time, certainly not the worsening one would expect with malignant tumor causing obstruction. I should think that the fluffiness would be more consistent with tuberculosis than with any other lesion. Therefore, I think that I shall stick by that diagnosis.

He undoubtedly had secondary infection behind the obstructed bronchus, which receded with therapy, I suppose.

DR. WILSON: There may have been more atelectasis in the ten day interval to account for the fact that the process appeared to improve.

DR. MARSHALL K. BARTLETT: I should like to ask if this were a tuberculosis process with all this cavitation, would it not be surprising that the patient was not sicker and did not have more evidence of a general systemic reaction?

DR. PIER: It is difficult to tell just how sick he really was. I suppose that this cavity could have been an abscess from secondary infection — a bronchiectatic abscess.

DR. F. THOMAS GEPHART: When he was sent in by his physician, he was perfectly well; there was no apparent weight loss.

DR. PIER: I think that he had a low-grade tuberculous activity in the periphery, with a sclerosed obstructed bronchus that resulted in collapse. I think that was the reason he was not sicker. If he had a severe pyogenic process, a tumor or a fungous infection, he would have been much sicker, I think.

DR. N. JOEL EHRENKRANZ: Perhaps the picture started with an acute Friedländer's pneumonia that was inadequately treated and formed miliary abscesses, with bronchiectasis in the right upper lobe.

DR. PIER: I suppose that is possible, but there is no clear-cut history of pneumonia. There was a long period of cough and brief episodes of fever.

DR. WILSON: If this was Friedländer's pneumonia, it would have had to be present for a long time before the first examination ten months previously. This is so because the process initially will cause overexpansion of the lobe rather than atelectasis.

DR. ROBERT S. PALMER: I should like to ask Dr. Pier if he would advise operation on this patient assuming it was tuberculosis? Is it customary and satisfactory treatment to operate on localized pulmonary tuberculosis? How extensive can pulmonary tuberculosis be and be called operable?

DR. PIER: I should certainly like to have the diagnosis of tuberculosis proved before the operation and I should want him well covered with antituberculosis drugs. I think that in a case where the bronchus is largely occluded by tuberculosis, with this degree of collapse and cavitation, an operation would have to be performed sooner or later.

DR. LAWRENCE H. WARBASSE: If it was tuberculosis, do you not think it would have been better to treat him and let him go home for awhile before operating?

DR. PIER: I think that I should have done that if the diagnosis was proved. I am a little surprised that the surgeons operated so soon.

DR. BENJAMIN CASTLEMAN: Perhaps we can ask the surgeon why he operated so soon. Dr. Gephart?

DR. GEPHART: We believed that tuberculosis was a possibility. This patient had studies of the sputum done during the previous hospitalization and also a direct smear at the time of bronchoscopy, all of which showed no tubercle bacilli. We did not believe that this was tuberculosis; we thought it was a chronic recurrent infection in the upper lobe as the result of obstruction of the bronchus by an enlarged lymph node or an old pneumonitis that had led to a destruction of the lung with gradual increase in atelectasis. I remember telling the family that although this might be a chronic infection, we certainly had to consider cancer in the upper lobe in a man of this age. He had repeated episodes of fever and if this was chronic pneumonitis, the upper lobe was destroyed, and it was only a matter of time until he had more trouble. Therefore we thought we should remove this part of the lung. If we had been sure he had tuberculosis or could have been sure he did not have cancer, it certainly would have been better to prepare him with antibiotics. He had one doubtful cytologic smear of the sputum which did not impress us, because we have seen cytologic reports of sputa that were doubtful and also positive in patients with chronic pneumonitis.

DR. WILSON: I read the films initially and I did not think it was tuberculosis because there was no evidence of disease in the lungs, other than in the right upper lobe. If he had this much atelectasis of the right upper lobe, it probably meant he had had bronchial tuberculosis at one time so that one would have expected additional involvement elsewhere in the lungs.

DR. CASTLEMAN: It was your conclusion, Dr. Wilson, that it was a nonspecific chronic inflammatory process, which is what most physicians believed that he had. We have seen a number of patients with a nonspecific chronic pneumonitis that went on in this fashion for months.

DR. PALMER: How often does it occur in the upper lobe apexes?

DR. CASTLEMAN: We have seen it in the upper

lobe, but not as commonly as in the middle or lower lobes.

Clinical Diagnosis

Chronic pneumonitis, right upper lobe.

Dr. Arthur S. Pier, Jr.'s, Diagnosis

Pulmonary tuberculosis.

Anatomical Diagnosis

Squamous-cell carcinoma of lung, right upper lobe.

Pathological Discussion

Dr. Castleman: Would you like to tell us what you found at operation, Dr. Gephart?

Dr. Gephart: At operation we found many firm vascular adhesions over the upper lobe, which was solid and shrunken. We believed that they confirmed the impression of a long-standing chronic pneumonitis. These adhesions were separated with considerable difficulty. When we freed the hilum, however, we felt a moderately firm lymph node along the upper lobe bronchus. Since we were still concerned with the possibilities of cancer and of tuberculosis, we removed this lymph node for a rush frozen section, which the pathologist reported to contain carcinoma. It was necessary to do a pneumonectomy and to take the vessels within the pericardium in order to remove the entire tumor.

Dr. Castleman: We found that the right upper lobe bronchus was obstructed by a mass which had apparently caused a backing up of fluid and inspissated material to form an abscess. In a smaller bronchus beyond the major one, tumor involved the mucosa — evidence that the tumor had apparently extended down submucosally. Eight out of 11 lymph nodes that we examined were positive for cancer; scattered throughout and in the abscess beyond the obstruction we found islands of tumor. This was a slowly growing squamous-cell carcinoma, with much more keratinization and maturity of squamous cells than is often seen in a squamous-cell carcinoma of the lung. This probably accounts for the fact that it did not grow much in ten months. It is the type of tumor that, even though the lymph nodes were small and involved, may have been entirely removed; and the patient may well have been cured.

Dr. Gephart: I think if this had been tuberculosis, the patient's being in such good condition, the absence of disease elsewhere and our inability to demonstrate tubercle bacilli, did not make it hazardous or poor practice to have removed the lobe at that time. Although in our thinking preoperatively we gave much less emphasis to tuberculosis than Dr. Pier did, still I think the possibility of cancer made it important to operate. If we had delayed another several months while trying antituberculosis chemotherapy this tumor might have been irresectable because it was just barely resectable at operation.

Dr. Castleman: This is the type of case in which pneumonitis associated with bronchiectasis beyond a tumor often clears and then returns. It is important to realize that the fact that an abscess in the lung or an area of pneumonitis clears, does not rule out carcinoma as the underlying process.

Dr. Palmer: How many smears of the sputum did you have?

Dr. Gephart: We had several, although he was not raising any sputum as I recall. We did have a smear of one washing from the bronchoscopy. It was doubtful but we did not put too much reliance on that report.

Dr. Palmer: What is the percentage of cytologic smears from bronchial washings positive for carcinoma that is proved?

Dr. Gephart: I think the sputum has a considerably higher percentage than the bronchial washings; I think that it probably runs around 75 per cent. It is also my impression that there have been a few false positives. I know of cases in which we have never been able to find evidence of a primary lesion even though the smears were positive. I do not think that is too surprising; if there is an infectious process, with epithelium that is continually healing, some of the cells may come off and be interpreted as malignant. Certainly a report of doubtful can be explained by chronic inflammation.

Dr. Castleman: The number of smears of the sputum that are falsely positive for carcinoma is very small. I think that when you have a smear that is positive for carcinoma from the sputum or from bronchial washings it is good evidence for carcinoma.

Dr. Palmer: Do you think it is 75 per cent? I seem to remember it as higher.

Dr. Castleman: Mrs. Ruth Graham of our Cytology Laboratory has informed me that a positive smear is obtained in about 65 to 70 per cent of all cancers of the lung. During 1955 the cytological examination of the sputum or bronchial washings of 30 cases has been positive and in every one of these cases the patient had cancer; in other words, so far this year there have been no false positive cases.

A Physician: I should like to ask the radiologist if he thinks that in this case a tomogram would have been helpful?

Dr. Wilson: Yes; I think it would have been.

Dr. Castleman: Since he had a completely obstructed bronchus that merged with the pneumonitis and abscess formation, it might have been difficult to distinguish between the tumor and the pneumonitis on a tomogram. We knew that the bronchus was obstructed anyway.

Dr. Wilson: We might have been able to have seen some of the enlarged lymph nodes.

Dr. Castleman: They were quite small; the one that was removed was not very large, was it?

Dr. Gephart: No; also the lymph nodes could have been enlarged on the basis of inflammation as well.

Dr. Wilson: That is true.

Dr. Gephart: Even at operation in many cases it is impossible to tell whether enlarged lymph nodes are inflammatory or filled with tumor.

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ATOMS FOR CHRISTMAS

AT this special season of the year, in an era when crisis seems to be chronic, the thought that there may yet be peace on earth to men of good will seems out of touch with reality. For man's patient industry in the manipulation of his environment has too often borne fruits not entirely to his benefit. Many of the gifts that the earth has yielded for the amelioration of his condition have had their reactionary elements, and he has sometimes found it necessary to resort to a form of fatalism in order to rationalize his predicaments.

Something in the nature of an analysis of these predicaments was brought out in a pamphlet by Everett Morse Baker, published by the American Unitarian Association not long after the incident at Hiroshima. In it the thesis is reaffirmed that many persons through the ages have fallen into the error of misinterpreting God and His function in respect to the universe. This misinterpretation has resulted in a form of evasive thinking — not only that man's destinies are controlled entirely from a higher level, but also that salvation can come from a mere acknowledgment of God's omnipotence and capacity for setting things to rights.

The idea of this omnipotence as being finally responsible for man's success in adapting himself to his planet suffers in the face of life's facts, however, and it may be that a divine concern with human destinies is only part of the general cosmic arrangement. It is more probable that in this general arrangement man must accept for himself a more dynamic role than that of relegating the final responsibility to a higher power.

Now that instruments of such widespread destructiveness have been acquired the escapist ideas held by so many that the final responsibility for man's actions are beyond his control must be revised. The anthropomorphic God that he has conceived is bigger and less tangible than he thought and does not fit at all into the classical pattern of an unpredictable and somewhat petulant deity or group of deities determining his fate according to the caprice of the moment or the size of the sacrifice.

To have a logical meaning in a world that man by his own ingenuity can make uninhabitable, God must be the indefinable unit, above man's capacity for comprehension and greater than man's thoughts have been able to conceive, for they still cannot encompass ideas beyond the human pattern. God is the power of creation, not a prosecutor or a sheriff; the unalterable spirit of the universe, not the presiding justice of history's busiest police court.

As a result of this indefinability the creative and directing force of the universe becomes more understandably the one God of Christianity, of Judaism and of Islam. Such a flexible concept strengthens a belief that the single goal of universal decency can be sought

by a multitude of people under different leadership but on adjacent and converging roads.

Man's ability to outlive the products of his ingenuity will depend not on letting his burdens and the responsibility for his decisions fall on the superhuman shoulders of a humanized God; it will depend on his assuming his share of the responsibility for himself and his world, uplifted by the spiritual comfort that his belief can bring him. As has always been the case in the only existence with which he has had any experience, his social awareness and his moral judgment will serve him better in the long run than will his muscular development or his technologic skills.

The race is not always to the swift nor the battle to the strong, and survival of the present dominant form of life will result not so much from the ability to destroy faster and more furiously than one's opponents, as from the capacity to conform to things as they are and help to shape them for the better. The effective strategy is to avoid battles when possible and to win campaigns, rather than to win battles and lose campaigns. The gifts of magi, whether of gold and frankincense and myrrh or of uranium, reach their full value when they are put to their proper uses.

POLIOMYELITIS: 1916-1955

Now that the 1955 epidemic of poliomyelitis in Massachusetts has passed by, its extent can be more calmly appraised than during the months of greatest threat — particularly in August and September. Then the newspapers were giving considerable prominence to the 1955 outbreak as being the worst ever recorded, even surpassing that of 1916. At first glance this seems true, when comparisons are made only on the basis of numbers of reported cases and with no regard for differences in severity of infection. Actually, there are several reasons to question the validity of the suggestion that the current outbreak outdid the infamous 1916 epidemic. In the first place the rationale of the reporting of nonparalytic cases had not been established in 1916, and "infantile paralysis" meant what the name implied — paralysis. Aycock's concept of poliomyelitis as largely due to a chain of inapparent infections was not to be formulated, let alone confirmed, for many years. Therefore, any comparison to be made in 1955 is logically confined to paralytic cases — the black bars of Figure 1. When this is done it is readily apparent that the 1916 wave surpassed the present wave in magnitude.

In the 1955 outbreak the build-up was rapid, and the epidemic curve skewed to the right. In 1916, on the other hand, the curve was skewed to the left, and the build-up was slow. It required some ten weeks for a persisting peak to be reached during late September and October, and substantial numbers of cases occurred in November. Some of the differences may be explained in terms of differences in transportation between 1955 and 1916. Certainly, everything conspires toward a quicker dissemination of a contact-spread disease today.

Evidence that a comparison based on paralytic cases only is valid — or at least far more valid than one based on total numbers of cases — is to be found in mortality figures since 1916. In the eighteen years 1917 through 1934 the death rate per 100,000 population from poliomyelitis was between 1 and 2 in half the years; the rate was under 1 in the other half. In

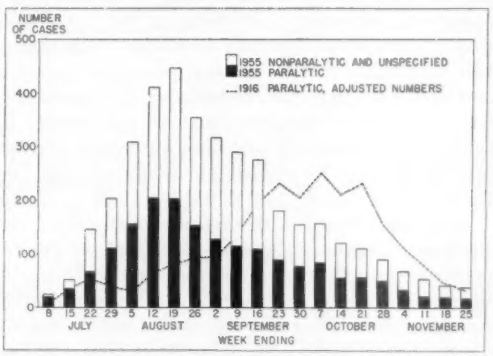

FIGURE 1. *Cases of Poliomyelitis, Paralytic and Nonparalytic, in Massachusetts, 1916 and 1955.*
In 1916 most of the cases are paralytic, the numbers being adjusted to the 1955 Massachusetts population.

the eighteen years 1935 through 1954 the rates were between 1 and 2 per 100,000 population in seven years and under 1 in eleven. The rates are relatively stable. Meanwhile, reported cases have been rising from less than 10 per 100,000 population in the early decades to over 10 per 100,000 in all but one of the last twelve years. In the four years 1917 through 1920, the rates were 4.8, 2.9, 2.2 and 2.4 respectively; from 1949 through 1952 the rates were 28.4, 22.0, 18.6 and 36.9. Either the disease is more prevalent or it is more widely recognized and reported. The stability of the death rates confirms what would be general clinical opinion — that it is the recognition and reporting of the illnesses that would have been allowed to pass unheralded in 1916 that swells the totals of today's counts. The record year is still 1916, and it may be hoped that the record will never be surpassed.

TRUSTEE-STAFF RELATIONS

PRACTITIONERS of medicine, by the very nature of their professional services, have been from the beginning relatively independent thinkers and workers. This independence has not always been well directed, but more and more they have learned the value of teamwork and have come to appreciate the necessity of organization. Accustomed as physicians are to accept grave responsibilities they still believe, with considerable logic, that they should also have a hand in

making the rules that govern the discharge of those responsibilities.

On occasion the independence of hospital staffs, composed of men and women trained in the care of patients, has been overborne by the authority of trustees who have applied to this sensitive area methods suggestive of business employment practices and are sometimes apparently addicted to the exercise of authoritarian discipline. The unfortunate controversy concerning which Dr. Bradford has written in the correspondence column of this issue of the *Journal* appears to represent a situation of this nature. In such disputes there is usually something to be said on both sides of the matter, and it appears that the members of the hospital staff, recognizing this probability, have sought free discussion and an opportunity for compromise, consonant with that autonomy so necessary for the exercise of their functions on a high professional level.

Such breakdowns in the delicate relations between the business of hospital management and the practice of medicine within hospitals can have only an unhappy effect on the purposes for which the institutions were founded. They can be avoided by a clear understanding of and a respect for the functions of each group by the other, working in close harmony and with mutual regard.

PROFESSOR G. H. MONRAD-KROHN

THE retirement of Professor Monrad-Krohn from the Medical School of the University of Norway was marked on September 24, 1955, by the presentation of a bust, which was erected on the grounds of the Rikshospitalet (Fig. 1). The ceremony, attended by 250 physicians and friends, marked an epoch in the history of neurology in Norway and indeed throughout the world. The name of Monrad-Krohn is known everywhere the English language is spoken, through his book, *"The Clinical Examination of the Nervous System,"* first published in 1921 and reaching its tenth edition in 1954. In addition, the work has been issued in both French and German.

FIGURE 1.

No student of modern neurology in modern times has not either owned a copy of Monrad-Krohn's book or had access to one. His influence, therefore, has been widely spread beyond the confines of his own university. By setting the highest standards of clarity in the complicated field of neurologic diagnosis, he wrote in simple, straightforward language in a manner easily comprehended by the average student of medicine. Throughout the years he kept his text entirely abreast of the times, and the book became with each new edition more valuable to generation after generation of students and practitioners. In addition, in his own clinic he elaborated an ideal neurologic unit intimately associated with neurosurgery. For over thirty years Monrad-Krohn has been a leader in the field of neurology, and now, having reached an age of retirement, he leaves a warm sense of gratification in the hearts of his colleagues throughout the world for the work that he has accomplished in teaching and through his book, his clinic and his personal standard of integrity.

[Doctor Afield] *We learn that Leonard Marsh, M.D., has been elected to the chair of Latin and Greek in the University of Vermont, and has accepted the appointment.*

Boston M. & S. J., *Dec. 27, 1855*

CORRESPONDENCE

TRUSTEES VERSUS STAFF

To the Editor: The relation between the trustees of a community hospital and the medical staff has never been clearly defined, and just now this issue is being critically tested. The outcome may be of the greatest importance. At the Mount Auburn Hospital, the trustees have contended that they are entitled to make bylaws for the medical staff and to impose them, with or without the staff's consent. The staff, although willing to abide by any legal regulations, has repudiated such an imposition of bylaws. This was voted by a 3:1 majority (54 to 18), by closed ballot, at the last staff meeting. If the view of the trustees prevails, it is obvious that not only these bylaws, but also any other changes that the trustees may choose to make at a later time can be legally enforced on the medical staff; doctors will then lose their independent professional standing altogether in relation to the hospital. They will assume the status of employees or licensees working in the institution.

From a legal standpoint there is no question that trustee dominance can be asserted in this manner, but the danger is that it may be asserted so arbitrarily, as in this case, that the medical staff loses its autonomy. To prevent such encroachment, the Joint Accreditation Commission of the American Medical Association, the American College of Physicians, the American College of Surgeons and the

American Hospital Association has established as a requirement for accreditation a specific rule that "the Medical Staff must be a self-governing body." Just how much latitude this term allows is not stated. It seems that the most elementary definition of "self-governing body" would include adequate elective representation on the staff's own executive committee. It also seems elementary that to be self-governing the staff should have the right to make, or at least to approve, its own bylaws. Both these points, however, are denied by the trustees. A tentative ruling has been received from the director of the Accreditation Commission sustaining the trustees in their position, as they have presented their case to him, but what final action the Commission may take after investigating both sides of the matter is not yet known.

Whatever the outcome may be at Mount Auburn Hospital, the question is now clearly raised for the entire medical profession: What are a doctor's rights in the hospitals in which he works and freely serves? If trustees exercise unlimited authority, two serious dangers to medical practice as we have known it may be foreseen: there will be unlimited opportunity for inexperienced, lay administrators to interfere in the medical decisions of hospital staffs, and the doctors will have no recourse or appeal from their decisions; and cliques of ambitious doctors, by gaining influence over trustees whose medical judgment is completely lacking, may dominate the administration of some hospitals to such an extent that independent practitioners will be handicapped or excluded from a normal, free use of the hospital. The medical facilities of a community may thus come to be monopolized by self-interested groups.

These matters may soon be referred to the Council of the Massachusetts Medical Society for full debate. It is important that doctors serving on hospital staffs everywhere realize how much is at stake. If they fail to take emphatic action now, they can only with difficulty later on regain the rights or privileges that they are losing.

CHARLES H. BRADFORD, M.D.

Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Psychoanalytic Study of the Child. Vol. 9. Edited by Ruth S. Eissler, M.D., et al. 8°, cloth, 369 pp., with illustrations. New York: International Universities Press, Incorporated, 1954. $7.50.

This new volume of a standard series contains 14 articles on various aspects of psychoanalysis in children. The material is divided into three sections: the problems of infantile neurosis; normal and pathologic development; and technic. There is a table of contents of the previous 8 volumes.

Clinical Electrocardiography. By David Scherf, M.D.; and Linn J. Boyd, M.D., associate clinical professor of medicine and professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals. Fourth revised edition. 8°, cloth, 490 pp., with 292 illustrations. New York: Grune and Stratton, 1953. $7.50.

In this fourth edition the book, first published in 1940, has been revised and brought up to date. (It is interesting that there are French, Portuguese and Spanish editions.) Extensive bibliographies are appended to the chapters. There is a good index; the printing was done in Great Britain.

Acta Geneticae Medicae et Gemellologiae. Vol. 3. (Maii, 1954–N.2.) Rome. Subscription per vol. $13.00.

NONCLINICAL NOTES

HEROIC, NO LESS

The following excerpt from the *Journal of the South Carolina Medical Association* shows how far this little candle threw its beam:

> The epic-making discovery of Pauling et al demonstrated that HgbS has a distinctive electrophoretic behavior. *N. England J. Med.* **253**:323. Sermons in stones, poetry in hemoglobin—

NOTICES

ANNOUNCEMENT

Dr. Melvin I. Klayman announces the opening of an office for the practice of gastroenterology and internal medicine at 475 Commonwealth Avenue, Boston.

HARVARD MEDICAL SOCIETY

A symposium on psychochemistry will be given by the Harvard Medical Society in the Amphitheater of Building D, Harvard Medical School, Tuesday, January 10, at 8 p.m. Dr. Harry C. Solomon will preside. The program is as follows:

Studies on Lipide Synthesis by Normal and Pathologic Nervous Tissue. M. L. Karnovsky and G. Majno.

The Effect of Psychotogenic Drugs on Behavior. Robert W. Hyde.

Neuropharmacological Aspects of Psychotogenic Substances. Max Rinkel.

Drugs Acting on the Brain Stem Reticular Formation. Dale G. Friend.

The Behavioral Manifestations of Commonly Employed Therapeutic Agents. Henry K. Beecher.

HARVARD MEDICAL SCHOOL "ARS MEDICA"

Through the courtesy of Smith, Kline, and French Laboratories, a medical art collection entitled "Ars Medica," on loan from the Philadelphia Museum of Art, is on exhibit at the Warren Museum, Harvard Medical School, through January 3, 1956.

The collection consists of eighty-five famous rare pieces of graphic art depicting the practice of medicine over the centuries. Included in the works are paintings by Rembrandt, Daumier, Goya, Hogarth and Toulouse-Lautrec.

The museum is open to medical students and physicians from 10 a.m. to 4 p.m. daily except Saturdays, Sundays and holidays.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be held in the Morse Auditorium, Museum of Science, Science Park, Boston, on Monday, January 9, 1956, at 8 p.m.

PROGRAM

From New England, James M. Faulkner, M.D., presiding:

The Rapid Colcrimetric Chemical Diagnosis of Pheochromocytoma and the Determination of Epinephrine and Nor-Epinephrine in Body Fluids and Tissues. Hirsh Sulkowitch, M.D., and Lewis Hurxthal, M.D.

The Physiological Effects of Long-Term, High-Dosage Estrogen Therapy on Adrenocortical, Testicular and Thyroid Function in Coronary Atherosclerosis. R. W. Robinson, M.D., N. Higano, M.D., W. D. Cohen, Ph.D., R. C. Sniffen, M.D., and J. T. Sherer, Jr., M.D.

Pressor Effect of Catecholamines in Normal and Toxemic Pregnancy As a Clinical Pre-Toxemia Test. W. Raab, M.D., G. Schroeder, M.D., R. Wagner, M.D., and W. Gigee, M.D.

Beth Israel Hospital, Herrman L. Blumgart, M.D., presiding:

The Therapy of Cardiac Arrhythmias by I^{131} Induction of Hypothyroidism. George S. Kurland, M.D., Paul M. Zoll, M.D., A. Stone Freedberg, M.D., and Herrman L. Blumgart, M.D.

The Mechanism of Anomalous Atrioventricular Excitation (Wolff–Parkinson–White Syndrome). Louis Wolff, M.D.

Experimental Studies in Venous Thrombosis and Pulmonary Embolism and Their Clinical Significance. Stanford Wessler, M.D., Leopold Reiner, M.D., and Jonathan D. Ballon, M.D.

The Effects of Orally Administered Protoveratrine A and Protoveratrine B in Arterial Hypertension: A striking difference in activity. Bertram M. Winer, M.D.

Free parking privileges are available on the premises at Science Park (emergency telephone number, RIchmond 2-1410).

Interested physicians and medical students are cordially invited to attend.

ATLANTA GRADUATE MEDICAL ASSEMBLY

The annual meeting of the Atlanta Graduate Medical Assembly will be held at the Atlanta Biltmore Hotel, February 20-22, 1956. Hotel reservations should be made well in advance. Further information may be obtained from Dr. Mark S. Dougherty, chairman, Publicity Committee, Atlanta Graduate Medical Assembly, 15 Peachtree Place, N.W., Atlanta, Georgia.

AMERICAN COLLEGE OF SURGEONS

The four-day sectional meeting of the American College of Surgeons will be held at the Bellevue-Stratford, Philadelphia, February 13-16. Dr. Calvin M. Smyth, Jr., is chairman of the local advisory committee on arrangements.

The meeting will feature sessions in general surgery and the specialties, hospital clinics, surgical-forum research reports, cine clinic films, technical exhibits and hospital field trips. A special four-day program for nurses will be included. Clinical sessions will be offered in the hospitals.

Further information may be obtained from Dr. H. Prather Saunders, associate director, American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 22–28. Consultation Clinics for Crippled Children in Massachusetts. Page 937, issue of November 24.

JANUARY 9. New England Cardiovascular Society. Page 1135.

JANUARY 9–14, 1956. Pan American Congress of Ophthalmology. Page 944, issue of November 24.

JANUARY 10. Harvard Medical Society. Page 1135.

JANUARY 13, 20 and 27 and FEBRUARY 3, 1956. Yale University School of Medicine, Yale-New Haven Medical Center. Page 1092, issue of December 15.

JANUARY 16, 1956. Hartford Medical Society. Page 708, issue of October 20.

JANUARY 16, FEBRUARY 6, MARCH 5 and APRIL 2, 1956. Fried Lecture Series. Page 535, issue of September 22.

JANUARY 20–27, 1956. Fifth Panamerican Congress of Gastroenterology. Page 746, issue of October 27.

JANUARY 25, FEBRUARY 29, MARCH 21 and APRIL 25, 1956. Massachusetts Heart Association. Page 623, issue of October 16.

JANUARY 25, MARCH 21 and APRIL 26, 1956. Phi Delta Epsilon Fraternity Graduate Club Program. Page 118, issue of July 21.

JANUARY 30–FEBRUARY 8, MARCH 19–28 and JUNE 4–13, 1956. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

FEBRUARY 2–22. Atlanta Graduate Medical Assembly. Notice above.

FEBRUARY 13–16. American College of Surgeons. Notice above.

FEBRUARY 15, MARCH 28 and APRIL 18, 1956. Greater Boston Medical Society. Page 208, issue of August 4.

MARCH 19–22, 1956. American Academy of General Practice. Page 1092, issue of December 15.

MARCH 24 and 25, 1956. American Psychosomatic Society. Page 260, issue of August 11.

MAY 2, 1956. Postgraduate Medical Institute. Page 487, issue of September 15.

MAY 3–5, 1956. American Goiter Association. Page 348, issue of August 25.

MAY 28–JUNE 1, 1956. European Symposium on Vitamin B. Page 578, issue of September 29.

JUNE 21–23, 1956. Society of Nuclear Medicine. Page 1092, issue of December 15.

JUNE 21–24, 1956. American Academy of Dental Medicine. Page 994, issue of December 1.

AUGUST 19–23, 1956. American College of Chest Physicians. Page 840, issue of November 10.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, DECEMBER 29

THURSDAY, DECEMBER 29

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, DECEMBER 30

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*1:00–3:00 p.m. Combined Medical-Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, DECEMBER 31

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference (Blood Clinic). Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JANUARY 2

Holiday

TUESDAY, JANUARY 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Medical Clinicopathological Conference. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Medical Clinical Pathology Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.

(Concluded on page xii)

"I've sold a good many cars, and I expect to be selling for years to come!"

"Old age" is getting harder to define. Some of today's working men and women can claim 40, 50, or even more years of experience in their fields—and they're still not ready to retire! To help keep such vigorous folks fit and on the go, many doctors prescribe GEVRAL, a potent dietary supplement prepared specially for geriatric use.

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Vitamin B_{12}	1 mcgm.	Ascorbic Acid (C)	50 mg.	Boron (as $Na_2B_4O_7.10H_2O$)	0.1 mg.
Thiamine Mononitrate (B_1)	5 mg.	Vitamin E (as tocopheryl acetate)	10 I. U.	Copper (as CuO)	1 mg.
Riboflavin (B_2)	5 mg.	Rutin	25 mg.	Fluorine (as CaF_2)	0.1 mg.
Niacinamide	15 mg.	Purified Intrinsic Factor Concentrate	0.5 mg.	Manganese (as MnO_2)	1 mg.
Folic Acid	1 mg.	Iron (as $FeSO_4$)	10 mg.	Magnesium (as MgO)	1 mg.
Pyridoxine HCl (B_6)	0.5 mg.	Iodine (as KI)	0.5 mg.	Potassium (as K_2SO_4)	5 mg.
Ca Pantothenate	5 mg.			Zinc (as ZnO)	0.5 mg.

Other Lederle geriatric products include: GEVRABON* Vitamin-Mineral Supplement Liquid with a wine flavor; GEVRAL* Protein Vitamin-Mineral-Protein Supplement Powder; and GEVRINE* Vitamin-Mineral-Hormone Capsules.

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(Additional advertisements on page xii)

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1. Overall, J. C.: Southern M. J. 47:789, 1954. 2. Editorial: New England J. M. 246:111, 1952.
3. Grayzel, H. G., Heimer, C. B., and Grayzel R. W.: New York St. J. M. 53:2233, 1953.
4. Heimer, C. B., Grayzel, H. G., and Kramer, B.: Archives of Pediatrics 68:382, 1951.
5. Behrman, H. T., Combes, F. C., Bobroff, A., and Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
6. Turell, R.: New York St. J. M. 50:2282, 1950.

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For the modification of measles and the prevention or attenuation of infectious hepatitis and poliomyelitis.

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WEDNESDAY, JANUARY 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. Bertram Selverstone, John F. Sullivan and Justin Hope. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Kenneth D. Blackfan Lecture. Passive-Active Immunization in Certain Viral Diseases. Dr. Joseph Stokes. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:00 p.m. Surgical Pathology Conference. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:15 p.m. Children's Medical Service Symposium. Clinical Illustrations of Current Therapy with Acute, Subacute and Chronic Nephritis and Nephrosis. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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Sessions to be held at Worcester County Sanatorium, St. Vincent Hospital and Worcester City Hospital.

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